# Neurology

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THE AMERICAN ACADEMY OF NEUROLOGY

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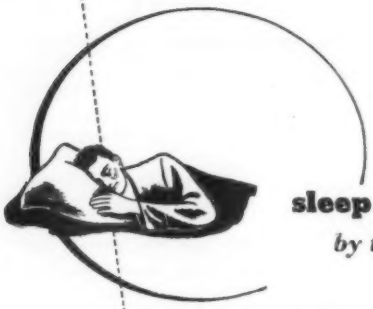

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# Neurology

## Cécile and Oskar Vogt

### On the Occasion of her 75th and his 80th Birthday

*Webb Haymaker, M.D.*

THE YEAR just past brought tributes from many lands to a pair of savants, Cécile and Oskar Vogt, who through several decades have played a significant role in advancing neurology to its present position. They reached as lofty a pinnacle as did the Curies, the Dejerines, the Nageottes. We join in extending them hearty congratulations in this, their jubilee year.

Cécile (Mugnier) Vogt was born on March 27, 1875 in Annecy, France, a town in the Province of Savoy where the inhabitants like to think that the blood of the Allobroges flows in their veins. Several of her forefathers were lawyers, but her father, Pierre Louis Mugnier (1809-77), broke the family tradition by becoming an army officer; he was attached to the *brigad de Savoie*, at that time Italian. He died of pneumonia when Cécile was only two. Cécile's mother was kindly, an independent thinker, and a woman of strong convictions. Certainly only a conviction of unusual degree could be read into the incident of Cécile's confirmation in the Catholic church: her mother, having separated herself from any participation in the church, escorted her to the portals of the cathedral but would not enter to witness the confirmation ceremony. An aunt of great wealth had planned from the beginning that Cécile should enter a convent and when Cécile was 13 she brought the subject

From the neuropathology section, Armed Forces Institute of Pathology, Washington, D.C.

to an issue. Cécile would not consent; she had decided to study medicine. Forthwith, Cécile's name was stricken from the aunt's will.

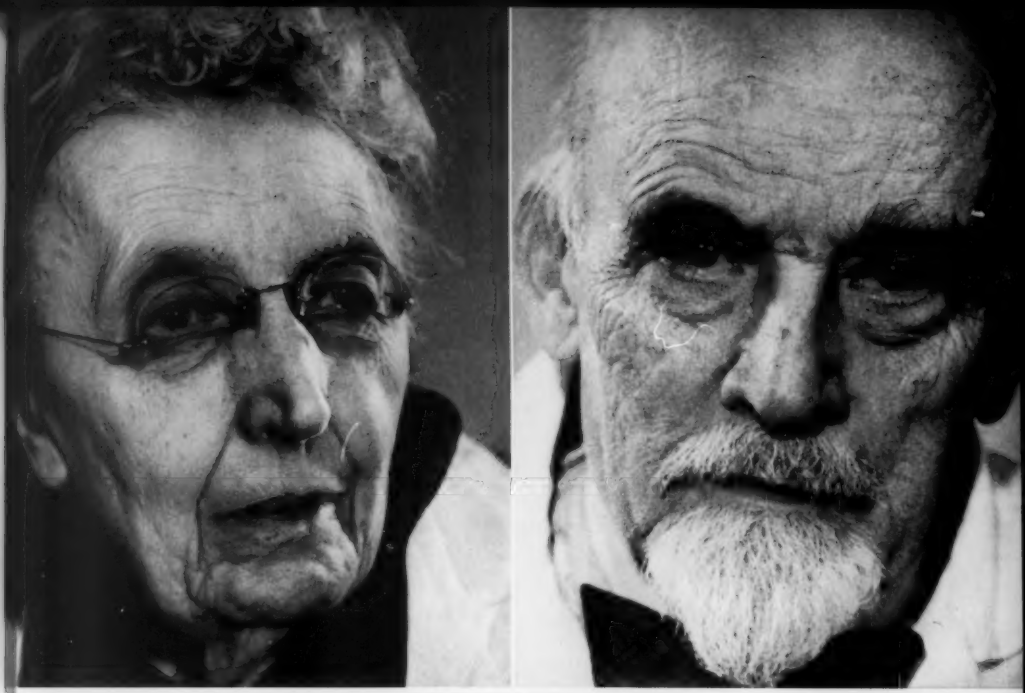
In 1893 Cécile Mugnier matriculated in the Faculté de Médecine in Paris. After completing the prescribed courses, she became externe (1896-97) and then, for a year, worked in the clinic of Pierre Marie at the Bicêtre. This was at a time when that distinguished pupil of Charcot was commencing a reform in the concept of aphasia and when, at the famous sessions of the Société neurologique, he made it a practice to pit one colleague against another in order to sharpen issues. It was during the year 1898 that she came to know a German student, Oskar Vogt, who had settled down at the Salpêtrière to learn clinical neurology under Dejerine.

Oskar Vogt-Dieckmann (he dropped the "Dieckmann" along the way) was born on April 6, 1870 in Husum, Schleswig, a town noted for its distinguished native son, the poet Theodor Storm. Oskar's father, Hans Friedrich Vogt (1835-79), a handsome man of scholarly bearing, was a woodsman and hunter before entering the ministry. He was a Lutheran, known far and wide for his liberal views, learned partly from his father, a landowner in Dithmarschen. Oskar's mother was half Danish; her mother had been a native of Copenhagen. Some of the men of the family were Lutheran ministers, others sea captains; and the family could boast of one pirate far back in their ancestry.

Already at the age of nine, Oskar had set his course: he had been an avid collector of postage stamps and had accumulated virtually all the

FIG. 1. (*Above*) Oskar Vogt at the age of three.

FIG. 2. (*Right*) His father, Hans Friedrich Vogt.



CÉCILE AND OSKAR VOGT

old issues of Schleswig, but now, feeling that this was a pursuit beneath his worth, he gave his stamps away so that he could embark unencumbered on collecting biologic items, such as birds nests, birds eggs and diatomes. He provided diatomes for the local dealer, who in return presented Oskar with his first microscope. At 16, Oskar began to collect bumblebees with the object of determining to what degree bumblebee races differed. The study of philosophy also took hold of Oskar during these years, and in this direction he owed much to his friend and teacher Ferdinand Tönnies who later was to make a name for himself in sociology and whose son, J. F. Tönnies, was to earn distinction as electroencephalographer in the Vogts' Berlin-Buch institute. In 1888 Oskar Vogt went to the University of Kiel as a student in philosophy, but after two semesters he turned to medicine. From 1890 onward Jena gave him his knowledge of biology and anatomy; here he was a student of Ernst Haeckel and later (1891-93) he became assistant to Max Fürbringer. During a subsequent assistantship (1893-94) to Otto Binswanger, in psychiatry, he completed his inaugural dissertation, entitled *Ueber Fasersysteme in der mittleren und caudalen Balkenabschnitten* (Leipzig, Veit & Co., 1894). Here is to be found a description of the fibers which penetrate the corpus callosum to reach the fornix, a discovery which, unbeknown to Oskar Vogt, had been made by von Kölliker six months earlier.

In the late spring of 1894, Oskar Vogt journeyed to Zürich-Burghölzi to work under the keen eye of August Forel. Arrangements for a stay with Forel had been made through a third party, but when Oskar Vogt arrived, Forel's memory thereof was completely blank.

"I have no place for you. But what do you want to study?" asked Forel after the formalities were over.

"Hypnotism and brain anatomy," replied Vogt.

"And what in brain anatomy?"

"More on the corpus callosum." And he added in his characteristically forthright manner, "Incidentally what you published recently on the corpus callosum is completely wrong. When the corpus callosum is absent, the defect is in the fibers which should have crossed the midline, not in the fasciculus occipito-frontalis, as you have written. Here are some sections I have brought along; I will show you."

Forel was angered inwardly that so young a man should display such effrontery, but years later he related the incident in his autobiography with some relish. Vogt stayed on for three months. From this association grew a lasting friendship and the establishment in 1902 of the *Journal für Psychologie und Neurologie*, which from the standpoint of illustrative material has never been surpassed.*

The problem of myelinogenesis was still an important issue in those days and hence Vogt proceeded to Leipzig to the fountain source, Flechsig. Here he remained until June, 1895. He decided to go to Paris to round out his knowledge of clinical neurology, but in order to obtain the financial means he accepted a well paying position at a spa in Alexandersbad in northern Bavaria. Here the wife of the elder Krupp became one of his patients and a friend; and it was here that he took as an assistant, Korbinian Brodmann, who had come to convalesce from an attack of diphtheria. Both were to play a significant role in Vogt's subsequent career.

Ward rounds and laboratory work with Dejerine during the year 1896-97 provided Oskar Vogt with a rich clinical background. Taking to heart a saying which he had learned as a schoolboy, "Schwör auf keines Meisters Lehre selbst nicht auf die von Socrates,"** he left Paris for Berlin to go his own scientific way. In 1898 he opened a Neurologische Zentralstation consisting of two departments: neuroanatomy and psy-

*This journal was a continuation of Forel's and O. Vogt's *Zeitschrift für Hypnotismus*. The illustrations in this new journal, mostly photographs, were of great documentary value because of their extraordinary size and clarity. They were reproduced in Oskar Vogt's printing plant in Berlin-Buch under his personal supervision. Publication of the journal came to an end in 1945, after the appearance of the 51st issue.

**"Swear by the teachings of no master, not even those of Socrates."

FIG. 3. (*Left*) Neurobiologische Zentralstation in the Berliner Mietshaus, Magdeburger Strasse.

FIG. 4. (*Below*) Cécile and Oskar Vogt in Berlin in 1902.

chology. Here Cécile Mugnier came in early 1899 to prepare her doctoral thesis. In March of that year they were married. Her thesis bore the title, *Étude sur la myélinisation des hémisphères cérébraux* (Paris, Steinheil, 1910); its dedicatory line reads, "Je dédie ma thèse à mon mari, qui m'a appris à travailler scientifiquement." The thesis finished, the Vogts journeyed to Paris in 1900 for the ceremony of conferment of the diploma of medicine on Cécile Vogt. While there they attended a meeting of the Société neurologique. Kattwinkel was to have presented a paper on the corpus callosum but was unable to attend, and his paper was read by Pierre Marie. Oskar Vogt rose during the discussion and criticized some points made in Kattwinkel's paper, whereupon Marie took exception to some of Vogt's statements. The next day the Vogts visited Marie at the Bicêtre, and one of his first remarks was: "Vogt you need some brains to study; here, take these thirty along back to Berlin." These brains became a part of the early Vogt collection, and to this day sections from them are to be found in Neustadt.

In 1902 the "Zentralstation" was incorporated into the University of

Berlin as the Neurobiologisches Laboratorium der Universität Berlin, but the new facilities were still small and the opportunities for work limited. As Oskar Vogt has related, the study of the structure of the brain was at that time in the hands of neurologists and psychiatrists, and that of neuropathology was largely under the jurisdiction of general pathologists who had neither the time nor the inclination to do the subject justice.[1] Therefore, the time was ripe for establishment of an institute which would bring together under one roof experts in the various disciplines concerned with the nervous system.

The Vogts, both talented organizers, set to work to fill this need. Their plan included the development of a brain reference library, where serially sectioned brains, both normal and pathologic, could be made available for study. It was not easy to obtain support for such an ambitious undertaking. Antagonism was encountered, and on one occasion when Cécile Vogt addressed a group of psychiatrists at their national meeting, one professor stalked out of the room in protest against her assertion that psychiatry could prosper only if more attention were given to neuropathology. Nevertheless, the Vogts continued in their campaign, and on January 23, 1915, their persistence was rewarded when their laboratory was placed under the aegis of the Kaiser Wilhelm-Gesellschaft zur Förderung der Wissenschaften. Financial support came from the Krupp family, the elder of which owed much to his friendship with Oskar Vogt.

So great was the progress of the Vogts along the course they had charted, that in 1931 a new and imposing Kaiser Wilhelm-Institut für Hirnforschung was opened for them in Buch, a suburb of northern Berlin. This site was chosen because it was in the vicinity of some of Berlin's largest hospitals. The institute was financed by contributions from the Kaiser Wilhelm-Gesellschaft zur Förderung der Wissenschaften, the Rockefeller Foundation, the German Reich, the State of Prussia and the city of Berlin. Its goals were clearly defined by Oskar Vogt.[2–4] The saying goes that when an investigator publishes an account of his new institute it is his last important publication. The Vogts proved exceptions. To make time for scientific work they gave up the strenuous private practice of neurology and psychoneurosis which they had carried on for years. Their publications have reached about 150.

In 1931 their staff numbered more than 100, of which about 30 were at the professional level. The organization of the institute into departments was as follows: anatomy, headed by Cécile Vogt; histology, Max Bielschowsky; experimental and electrophysiology, A. E. Kornmüller (now in Göttingen); engineering and electronics, J. F. Tönnies (now in Freiburg), and later J. A. Schraeder (now in Stuttgart); human physiology, M. H. Fischer (now in Berlin); animal genetics, N. Timoféeff-Ressovsky (now in Russia); clinical research (human genetics), B. Patzig (now in Marburg);

psychology, Irmgard Leux (now in Stockholm), and later W. Hochheimer (now in West Berlin); phonetics, E. Zwirner (now in western Germany); chemistry and pharmacology, Marthe Vogt (now in Edinburgh); photography, E. Heyse (now in Göttingen); and clinic and 60 bed hospital for selected patients, G. Soeken (now in Berlin).

FIG. 5. The Kaiser Wilhelm-Institut für Hirnforschung in Berlin-Buch. To the left and behind the main building is the nerve clinic; directly behind, the Director's home; to the right an apartment house for the staff; and behind, in the distance, the stables and garage.

From his student days, Oskar Vogt had been concerned with the problems of evolution and of brain-psyche (Gehirn-Seele) relationships. In the 1890's his interest in the former had been stimulated through his contact with Haeckel and in the latter by his association with Forel. As time went on it seemed to him that human ills could be elucidated through the study of animal genetics, but facilities for such a pursuit were not yet available; hence he and Cécile concentrated their attention on brain-psyche problems. Their hope that they would be able, through animal experiments, to cast some light on mental problems in man, particularly neurotic manifestations, was short-lived, however. Treatment of neurotic patients from a psychologic standpoint was of no real help. It seemed to them that predisposition in the somatic realm was important in the causation of the psychopathies; and hence they changed their approach so as to bear on "the phenomena of consciousness and the correlation of these phenomena with the material processes in the brain."[5] Their aim, then, became the study of the localization of function in the brain. Neuroanatomy, neuropathology, and the other cognate disciplines were to the Vogts merely the means to this end, not goals.

Having forsaken the psychologic approach to the study of that organ which "erst den Menschen zum Menschen mache," the Vogts turned to

the investigation of the myelinated fiber systems of the brain. It was at about this time (1904) that Elliot Smith published his work on myeloarchitecture, using for the purpose fresh unstained brain sections; he distinguished about 40 cortical fields separated by sharp boundaries. The Vogts' main objective was to determine the origin of fiber systems reaching certain parts of the grey matter, in an effort to find anatomic subdivisions of the brain which would have physiologic meaning. Toward this end they traced myelin degeneration in focally diseased or damaged human brains and in animal brains subjected to various lesions. They also employed Flechsig's myelogenetic method but disagreed with some of his fundamental observations, particularly in regard to time of myelination of certain tracts, and in general, found the method ill suited to their purpose.[6-10] They recognized in the cerebral white matter of fetuses and newborns a much more abundant subdivision of the strata into myeloarchitectonic fields than had previously been supposed, and in strongly differentiated myelin sheath preparations of adult man they were able to distinguish a number of myelogenetic fields, using as their criteria for time of myelinzation fiber density and thickness of myelin sheaths. They also showed in regard to many of the myeloarchitectonic subdivisions that adjacent fibers in the same stratum extend to different parts of the cortex.[9-14]

The systematic study of myeloarchitecture on which they were launched was made subordinate in the early 1900's to a broader investigation. There were two objectives. One was to analyze the arrangement, number, size and form of nerve cells within the laminae of the cortex (cytoarchitecture) and the corresponding relationships of the myelinated nerve fibers (myeloarchitecture) with a view to subdividing the brain into regions of specific structure, i.e. into fields (architectonics). Sixty-six "elementary topistic alba" were found in the frontal lobe alone.[13, 15] The other objective was to determine the interrelationships of different fields. In the course of these studies they continued to trace the origin and destination of elementary myelin fiber systems in myelin and Nissl preparations, in the latter of which they were able to distinguish centrifugal, retrograde and transneural degeneration. Oskar Vogt's first paper on cytoarchitectonics appeared in 1903.[8] In others that followed it was shown that myeloarchitectural fields correspond to cytoarchitectural fields.[16, 17]

Most of the work on cytoarchitectonics was assigned to their associate Korbinian Brodmann (1868-1918),[18] who during the period 1901-10 was largely instrumental in establishing the basis on which the present-day science of cytoarchitectonics of the mammalian cortex rests. It is of interest that the initial publications of Oskar Vogt,[8] Brodmann[19] and

Alfred Walter Campbell (1868-1937)[20] on cortical cytoarchitectonics all appeared within the year 1903. Brodmann's well known map of the human cortex was published in 1907,[21] and his concept of the fundamental six-layered "homogenetic" cortex,* based on embryology, was described in his famous monograph published in 1909.[22] Elliot Smith's[23] map of the human cortex, based on macroscopic studies, appeared in 1907. Oskar Vogt introduced the terms "allocortex" and "isocortex" in 1911,[14] and further elucidated "omnilaminäre" differences in the various fields in an important paper in 1919.[11]

The allocortex, except for some areas, is "heterogenetic" in the sense in which Brodmann employed this term. It includes predominantly the rhinencephalon and corresponds, according to von Economo and Koskinas,[24] to the paleocortex and archicortex of comparative anatomy (Edinger and Ariëns Kappers). The isocortex, under which the Vogts included their "eurädiären" and "infrarädiären" myeloarchitectonic types,[11] is "homogenetic," i.e. it shows the seven-layered fundamental pattern or an ontogenetic modification thereof. The isocortex of the Vogts constitutes the major part of the cortex of man and corresponds to the neocortex phylogenetically.

The importance of Brodmann's and the Vogts' work, and of Campbell's and Elliot Smith's as well, cannot be overemphasized, for prior to their time the knowledge of the structure of the cortex was shrouded in darkness, with only the pioneer studies of Meynert,[25] Betz,[26, 27] Hammarberg,[28] von Kölliker,[29] and Ramón y Cajal[30] available, and these were, at least in some respects, desultory. Some of the "hair-sharp" boundaries** between cortical topistic units (fields, arëas) described and illustrated by Brodmann and the Vogts could not be verified by others,[24, 32] Brodmann's views on embryologic stratification have been challenged,[33, 34] and the Vogts' line marking the transition from area 4 to area 6 may be a little too far forward,[35] but their work remains, nonetheless, a remarkable contribution.

But morphologic studies formed only a part of the Vogts' investigations. For a period of 15 years, starting in 1903, physiologic mapping of the cerebral cortex in monkeys was routine with them. Their working hypothesis was that physiologic differences must be reflected structurally.[2, 15, 37a, 39] The 200 or more different cortical fields ultimately delineated by them were believed to possess an equivalent number of functions, and

*Seven according to Oskar Vogt,[17] who contended that Brodmann overlooked the deepest lamina.

**The Vogts[31] have given a brief account of a trip to Munich in 1916 to attend the opening ceremonies of the founding of the Deutsche Forschungsanstalt für Psychiatrie. Here they met Franz Nissl (1860-1919), invited him to their hotel room, where, for hours, they showed him photographs of their cytoarchitectural fields. Nissl, who in his work on rabbits had concluded that cortical fields merge gradually with one another, finally declared, "Ich bin jetzt von den scharfen Grenzen der Felder überzeugt. Ich weiss nun, was Sie Architektonik nennen." ("I am now convinced of the existence of sharp boundaries between fields. I know now what you mean by architectonics.")

it was the interworking of these in myriad combinations—with each field subject to individual variation—which was believed to account for the myriad variations in human behavior. Their hypothesis found abundant support from stimulation experiments of those parts of the cortex in which function is demonstrable.[11, 16, 17, 36-37a]

They mapped altogether about 25 functionally different fields, each of which was shown to have its peculiar cytoarchitectural structure.[11] The magnitude of their work can be appreciated when it is considered that the functions of only six or seven regions of the cortex were known when the Vogts commenced their work. Subsequently support for individual functional differences in the various cortical fields was achieved through electroencephalographic studies by J. F. Tönnies and A. E. Kornmüller, both of whom began their work at Berlin-Buch shortly after Hans Berger had given electroencephalography its new impetus. It was while working in the Vogts' institute that Tönnies invented the polyneurograph.

In 1919 Otfrid Foerster began the mapping of the human cortex by means of electrical stimulation and for the next few years had frequent contact with the Vogts. In 1926 the Vogts completed the functional mapping of the cortex of the cercopithecus monkey;[11] and on the basis of this work and from their knowledge of the cytoarchitectural fields of man they drew up a functional map of the human cortex as they thought it should be. Foerster and Oskar Vogt agreed that on a certain day each would mail his map to the other to see how closely they would correspond. The maps differed only in small detail,[39] and in these Foerster conceded ten years later[38] that Vogt was correct. The field numbers employed by Foerster were those previously used by the Vogts. In a moving biographical sketch of the Vogts, Karl Kleist said of Oskar Vogt: "Sie hat O. Foerster's Reizversuchen an der menschlichen Hirnrinde zugrunde legen und bildet auch die anatomische Grunde *meiner* klinischen Gehirnpathologie."*

A few concrete examples of their physiologic findings may be cited. By means of electrical stimulation of the cerebral cortex of a variety of animals, from marsupials to orang-utan, they were able to delineate in all forms the "main excitable cortical area" ("Hauptfeld"; "Primärfeld"), since referred to as the "motor cortex," and the "indirectly excitable cortical areas" ("Sekundärfeldern"),[11, 37] since called the "premotor cortex." In a monograph published in 1907[37] it was shown that the somatotopic cortical pattern varied with the animal form. The ateles, for in-

*"You have laid the foundation of O. Foerster's electrical studies on the human cerebral cortex and you have provided the anatomic basis for my own work on applied brain pathology."

stance, with a tail capable of the most skillful movements, had a large cortical representation of the tail, whereas in the kangaroo, which uses its tail primarily for the purpose of locomotion, the representation was small. Bats, they found, had in addition to the motor area an easily excitable area in the temporal lobe, and from this and other observations they postulated that the perception of distant objects without the aid of vision is an auditory function. The view is closely in line with the present-day knowledge that bats control the direction of their flight by means of the radar effect of their supersonic squeaks.

Work on 150 monkeys reported in 1919[11] showed that both isolated movements (tonic specialized movements via area 4) and complex movements (adversive and postural movements; i.e. turning of the eyes and head to the opposite side) could be elicited by stimulating area 6a alpha* of the intact cortex. After this area had been separated from area 4 by an incision, isolated movements no longer could be aroused by electrical stimulation of area 6a alpha, and when area 6a alpha was undercut, the complex movements were abolished. From these results the Vogts concluded that isolated movements were performed through the intermediation of area 4 and that the complex ones were mediated through a separate corticofugal pathway emanating from area 6a alpha. This was the first demonstration of the extrapyramidal motor cortical field. Another outcome of their investigations was the discovery of the phenomenon of cortical suppression, masticatory movements induced from area 8b alpha ceasing when area 8 gamma was simultaneously stimulated. This work, reported in 1919,[11] seems to have escaped the notice of some who are now cited as the pioneers in this field. Some further details regarding the differentiation of cortical areas by their responses to electrical stimuli were later added by their daughter Marthe in 1933.[43] She was also responsible for demonstrating that certain pharmacologic agents introduced into experimental animals become equally distributed throughout all the grey matter.[44, 45] From this, Cécile and Oskar Vogt concluded that the isolated effects thus produced could be explained only on the basis of the differential topical reactivity.[3b]

The concept of topistic units was carried over by the Vogts into the field of neuropathology. Individual characteristics within topistic units were held responsible for their varying predisposition to succumb to a great variety of noxious agents and to genetic defects. As a designation for topistic vulnerability, Oskar Vogt coined, in 1922,[47] the word "pathoclisis." ("Unter *Pathoklisis* verstehen wir die Erscheinung dass auf eine

*On the basis of cytoarchitectural studies, Oskar Vogt subdivided Brodmann's area 6 into areas 6a alpha and beta and 6b.

*diffus* wirkende Schädigung nur ein Teil des Organismus mit einer pathologischen Veränderung reagiert."*) The Vogts reasoned that since topistic units function differently, each must have its peculiar physiochemical properties, the nature of which determines its pathoclisis.[31, 46-51] The pathologic anatomy of topistic disease, then, was expressed in terms of "pathoarchitectonics."[17, 47] For instance, Spatz's observations that the occurrence of iron and fat in glia cells is restricted to the globus pallidus and that the deposition of pseudocalcium occurs in pallidal vessel walls[52, 53] were taken by the Vogts as evidence that the globus pallidus has a special metabolism. The tendency for the globus pallidus to bear the brunt of the attack in carbon monoxide poisoning, Sommer's[54] sector and Bratz's[55] sector of the hippocampus in hypoxia, and the zona compacta of the substantia nigra in postencephalitic parkinsonism, was to them more readily explicable on this basis than on peculiarities of vascularization, of which they could find none of real significance in the nutrient arteries concerned.[31, 56] Spielmeyer, on the other hand, emphasized the importance of local functional disturbances in circulation as the basis of selective damage in certain parts of the brain, for instance in the hippocampus in the anoxia occurring during epileptic attacks.[40] Both were for the most part correct, but they could never harmonize their views; even today the problem of topical hypoxia of vascular origin versus pathoclisis in the Vogt sense cannot be considered settled.

The Vogts' concepts on pathoarchitectonics were applied also in the field of diseases of the basal ganglia, with which their names, especially Cécile's, have been indelibly linked.[31, 57-62] Distinct advances were made when they designated the caudate nucleus and putamen (a topistic unit) as the "striatum" and the globus pallidus as "pallidum"[59, 60, 63] and when on the basis of their pathologic studies they distinguished between a striatal syndrome (hyperkinesia with increased automatisms) and a pallidal syndrome (poverty of movement).[59] The characteristics of the glia pattern (gliaarchitectonics) and the vascular pattern (angioarchitectonics) of the basal ganglia were first mentioned by them. As early as 1909,[64] Cécile Vogt's atlas on the myeloarchitecture of the thalamus of the monkey appeared. Forty different grisea were distinguished. This was a pioneer work on myeloarchitectonic subdivision of the thalamic nuclei, based partly on degeneration studies following destruction of the medial lemniscus and brachium conjunctivum.** Resuming their study of the

*"By pathoclisis we mean the phenomenon that only a part of the organism undergoes pathologic changes when the entire organism is exposed to a noxious agent."

**This was Cécile Vogt's *pièce de résistance*. When asked what she considered her best work, Cécile Vogt replied: "That study of the thalamus in 1909; then there was that work on status marmoratus in 1911, but that was much simpler; oh– it is impossible to answer such a question."

problem of thalamic subdivision in 1941, the Vogts[65] concentrated on the centre-médian nucleus ("Centrale thalami") of man, which had been neglected since its first description by Jules Bernard Luys in 1865.[66] They found that the lateral (parvocellular) part of the nucleus projects to the putamen, and the medial (magnocellular) to the caudate division of the striatum. Another observation was that the centre-médian nucleus may undergo striking atrophy in old age.[65]

The important work of Cécile Vogt on *athétose double* appeared in 1911 in four communications,[63, 67-69] one in collaboration with Oppenheim, another with Freund. The following year saw the publication of Kinnier Wilson's great contribution on the striatum;[70] in it he was quick to acknowledge that "the syndrome published by Madame Vogt is the first in which the main function of the corpus striatum, as I believe, has been differentiated from that of the pyramidal system, and it corroborates to a considerable extent the views which I have formulated independently. . . ."

The story of how the first case fell into Cécile Vogt's hands is an interesting one. Oppenheim, close friend of the Vogts, had had under his care a young lady of 23 and her mother, both affected with bizarre movements. He had made the diagnosis of hereditary pseudobulbar palsy and postulated that the responsible lesion lay in the more caudal part of the operculum. The young lady died during childbirth. No lesion being found postmortem, Oppenheim telephoned Cécile Vogt asking whether she would care to examine the brain. She accepted, and when the brain was sectioned in Oppenheim's presence the striatum was found atrophied bilaterally. Oppenheim, purely a theorist so far as brain anatomy was concerned, hardly knew putamen from thalamus, and hence his contribution to the subsequent report was restricted to clinical description. Another case, that of a 77 year old woman without known family incidence of the disorder, was received from C. S. Freund, clinical neurologist in Breslau. In a publication which dealt with both these cases,[69] Cécile Vogt reported that the caudate nucleus and putamen were shrunken and contained focal feltworks of myelinated fibers. These foci gave the caudate nucleus and putamen a marbled or mottled appearance, for which reason Cécile Vogt named the disorder, *état marbré*, or *status marmoratus*. Since blocks from these brains had been chromated, cell studies could not be performed. Hence there was no way of determining whether glia had proliferated.

Somewhat more than a decade later, Scholz[71] reported athetosis in two sisters, commencing at the age of ten and eleven months respectively. The disorder had begun in one sister after trauma and in the other follow-

ing a bout of fever, from which Scholz concluded that the cause was exogenous. Postmortem study disclosed typical status marmoratus; the myelination had occurred in foci of glia proliferation. Max Bielschowsky (1869-1940), an associate of the Vogts from 1904 to 1933, also concerned himself with the problem of status marmoratus, and in a lengthy report in 1924[72a] of a case in which the pathologic changes were virtually unilateral, expressed the view that, "So geht aus diesem Fall fast noch einwandsfreier als aus dem Scholzschen hervor, das der Status marmoratus des Striatums den Abschluss eines im postfötalen Leben durch exogene Schädlichkeiten zustande kommenden Prozesses bilden kann."* In 1938 the paper by Scholz, Wake and Peters[72] appeared in which evidence was provided that the myelinated scars in status marmoratus were the consequence of hypoxia resulting from circulatory disturbances, for instance during difficult births.

The development of an excess of myelinated fibers in a region where the parenchyma was damaged was indeed an extraordinary finding, for up to that time it was agreed that nerve elements of the central nervous system do not regenerate. When Bielschowsky showed that a feltwork of myelinated fibers ("plaques fibromyéliniques") could be laid down in the cerebral cortex and striatum in general paralysis, the doubts that exogenous factors were important were dispelled, though not in certain quarters.[73] While Scholz (and later, Spatz[73a]) considered the myelinated fibers in status marmoratus to be a product of hyperregeneration, Bielschowsky favored the view that owing to alterations in the ground substance, myelin was laid down on naked (or myelin-poor) axis cylinders already present. Like Cécile Vogt, Max Bielschowsky thought that some plaques fibromyéliniques could be the products of dysgenesis. On this subject there are several works available.[57, 58, 60-62b] At the present time the Vogts feel that status marmoratus is always due to exogenous factors.[62a] A translation of their recent statement on this point goes as follows:[62b]

"As a consequence of blood vessel damage, blood plasma can escape into the neighboring brain tissue, causing it to be digested. The parenchyma is primarily affected. The resulting destruction of nerve cells was called 'cytolysis' by us as long ago as 1922. If the damage remains restricted to the parenchyma a proliferation of the glia, especially the oligodendroglia, occurs. This condition as well as the following was described by Alzheimer (1897) as 'perivascular gliosis.' Later, adjacent

*One may conclude that this case furnishes even more conclusive evidence than Scholz's that status marmoratus of the striatum develops as a consequence of exogenous damage incurred in postfetal life."

nerve fibers begin to sprout and to grow into this region, and then become covered with myelin sheaths. In this manner there develops a *perivascular hypermyelination* of the same kind as found in the myelinated feltworks of *plaques fibromyéliniques* of C. Vogt and of status marmoratus of C. and O. Vogt (1937;[31] see page 183). When the digestive action of the plasma is greater the glia cells also are destroyed and in the process their nuclei often display transitory pyknosis. The devastated tissue may finally be resorbed, with the result that only fluid-filled tissue spaces remain."

There were other disorders which the Vogts were the first to describe. One was a nonprogressive hyperkinetic motor disorder, of striatal origin, which they called *status fibrosus*.[58] Pathologically there was a steady disappearance of nerve cells, which led to shrinkage of the striatum and, as a consequence, to a closer approximation of the preserved myelinated nerve fiber bundles; gradually the myelinated fibers disappeared, leaving the striatum a glial scar. There were other cases, pathologically similar, in which the clinical course was steadily downhill. Cases of this category, of which Huntington's chorea was an example, were referred to as *status fibrosus progressivus*.[58, 60] Another disorder was *status dysmyelinisatus*, first described by the Vogts in 1919,[59] and in more detail in 1920.[60] Clinically it was allied to athetosis but the course was progressive. The globus pallidus and corpus Luysi were demyelinated bilaterally. Cécile Vogt coined the term *status praecribratus*[60] to designate a striatal disorder in which there was widespread pericapillary destruction of nerve cells, myelin and glia. This condition was shown to be the early stage of *status cribratus* (a term credited to Durand-Fardel)[73b] and to constitute the substrate of senile tremor; here the perivascular spaces were somewhat widened and the surrounding parenchyma damaged, with the result that small tissue gaps had occurred. *Status spongiosus* (thus named by A. Jakob?) was also given much attention by the Vogts. In this condition the perivascular spaces were greatly dilated, vessel walls were hyperplastic and distorted, and the surrounding parenchyma was converted into a spongy mass. Wilson's disease and extreme forms of general paresis were included under this category.

The Vogts' many observations on the striatum and pallidum were brought together in monograph form in 1920[60] and again in 1936.[31] These were classic works in which it was clearly shown that disease processes of different etiology but of similar location may cause much the same clinical picture. The 1920 article also contains a description of striatal connections much as we know them today, except for direct corticostriatal pathways which they felt were too ill-defined to include. Of the

1936 article, Oskar Vogt once said, "Das ist vielleicht das Beste was ich über die Pathoklise geschrieben habe."*

These, then, are the main contributions of the Vogts and their pupils. Years will be required to plumb the depths of their work.

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Throughout their careers the Vogts travelled widely. Their object, if they were not lecturing, was to collect bumblebees and beetles. In insect catching they were, and still are, as avid as Forel and Julian Huxley in the pursuit of ants. Their selection of parts of the world to visit was always determined by the interest these places held as potential insect haunts, and the time of the year for vacation had to coincide with the season when the bumblebees and beetles were young, numerous and in perfect condition. The beauties of nature, which under ordinary circumstances would have delighted them, went unheeded when hot on the trail of some rare indigenous species. Mountain climbing fascinated them, but only to the height where these insects dwelt. Whenever there was a chance of finding bumblebees, they would stand for hours beside flower beds to capture their victims. Cécile Vogt, always devoted to her husband's interests, would hold the cyanide bottle ready, and when the bumblebees had breathed their last she would start mounting the catch on fine pins. To Asia Minor, North Africa, Spain, and the Balkans they went on their quest; and they always made a practice of returning to Berlin in time to round out their vacation with a trip to Paris.

Forel's chief interest in studying ants was to determine race differences from the standpoint of behavior. This was a subject which had always greatly interested him for he felt that one could be successful in studying human behavior from the psychiatric standpoint only if racial differences were taken into consideration. One day he took Oskar Vogt on a short trip to demonstrate racial differences in ants. He plunged his hand into an ant hole and brought it out again and there was not an ant on it. The whole colony then began a mad scramble to escape. A little further on he repeated the performance; this time his hand was covered with ants savagely attacking him. Oskar Vogt's object in studying bumblebees and beetles was altogether different. He was interested in the laws underlying variations and thus concentrated on the variations of the color bands in bumblebees and in the size, shape and position of color spots on the wing apparatus of beetles. He contended that just as the body hair and color

*"That is perhaps the best work I have written on pathoclisis."

spots of these insects are subject to variation, so also is the brain of man subject to structural variation, even so far as individual laminae of a cortical area were concerned.

When Oskar Vogt became director of the Institute at Berlin-Buch he insisted that a department of insect genetics be set up, and he introduced into that department the use of small beetles (Epilachna chrysomelina) for studies on race formation. These studies served as the bulwark of his and Cécile's theory of pathoclisis, which later was crystallized when applied to diseases of man.[31, 49, 74]

Naturally recognition and honors came to them. Both received the Moebius Prize (1921), and both were accorded honorary doctorates by several German universities. Oskar Vogt was the recipient of the Erb medal (1926) and the Kraepelin gold medal (1928) and was made Doctor h.c. and later Professor of Medicine h.c. of the University of Porto, Portugal (1921) and Doctor h.c. of the University of Wilno, Poland (1925). In 1950 two more honors came to him: one the National Prize of 100,000 Ost Marks bestowed by the Deutsche Akademie der Wissenschaften zu Berlin, in the Russian Zone of Berlin; and the other the conferment of the Honorary D.Sc. by Oxford University.* When Lenin died in 1924, the Russian Government called Oskar Vogt to Moscow, commissioning him to examine Lenin's brain and to set up a Brain Research Institute. For this purpose an old mansion, once belonging to an industrialist, was selected. Among those who joined the staff were some of the Vogts' former pupils: S. A. Sarkissow, I. N. Filimonoff, I. D. Sapir, and I. and N. Popoff. Oskar Vogt went back and forth to Moscow until 1929, when he delivered an address in which the unusual nature of Lenin's brain was referred to.[75] The Vogts never saw the newly-erected Moscow Institute.

Politically their sympathies were such that with the upsurgence of the Nazi party, Oskar Vogt was forced to retire from the directorship of the institute. Given the privilege of selecting his successor, he chose Nissl's pupil Hugo Spatz, who became director on April 1, 1937. The general tenor of the institute changed somewhat, there being a closer orientation with neurosurgery (W. Tönnis being placed in charge of that department), neuropathology (with Hallervorden the chief from the establishment of the department in 1937), and general pathology (through Anders,

*On this occasion the Public Orator delivered an address in Latin. He referred to Oskar Vogt as the "Nestor of Neurologists." The oration began with these remarks: "The poet Ennius once declared that he had three souls. Dr. Vogt, I think, has the same number—for *Jena* taught him his anatomy; a famous *Swiss* neurologist, August Forel, was his next instructor; and his clinical neurology was learned from the *French*, who also gave him his wife, a companion to share his work and his honours."

Prosektor of the Bucher Krankenanstalten). The department of physical chemistry, in which problems of brain edema, etc., were pursued, was taken over by H. Selbach (now in West Berlin).

Not to be thwarted in the pursuit of their studies, the Vogts built a private institute in Neustadt, deep in the Schwarzwald some 20 miles up the Höllental valley from Freiburg i. Br. It was named the Institut der Deutschen Hirnforschungs-Gesellschaft m.b.H. Krupp von Bohlen und Halbach (successor to the elder Krupp) helped to finance the Institute. The Vogts took with them the main part of the brain collection and the insect collections.* They were allowed to work unmolested, though at the beginning of World War II, Oskar Vogt, then 69, was drafted into the army as a private and placed in charge of organizing the military hospitals near Neustadt. Inasmuch as he had to give orders to officers, he was instructed to cover his private's uniform at all times with a white coat. He served in that capacity for six weeks, until the ridiculousness of the situation became so glaring that he was discharged from the army.

The neurologic collection, which was subsequently accumulated by Spatz and his associates at Berlin-Buch, did not meet so happy a fate. When the bombing of Berlin became heavy in 1944, Spatz induced Hallervorden to move part of the collection, including some of the library, to an improvised Institute in Dillenburg (Nassau). After the destruction of his neurosurgical clinic in Berlin, Tönnis transferred his activities to Ischl, Austria. In early 1945, Kornmüller moved to Göttingen, and Patzig to Schleswig. Finally, in latter March, 1945, when the armies from the East were advancing threateningly toward Berlin, Spatz managed to pack many valuable materials into 70 large boxes and place them aboard a freight train, with Munich as the destination. The greater part of the library and the entire museum collection had to be left behind. The materials reached Munich in a rather damaged condition, and were taken to the Deutsche Forschungsanstalt für Psychiatrie, of which W. Scholz was, and is now, director. In 1947 the collection was dispatched to Dillenburg, where, after a three year separation, Spatz and Hallervorden were reunited. In 1948 the Max-Planck-Institut für Hirnforschung was founded in the western zone of Germany. Up to the present it has not been possible to assemble all its departments under one roof. Spatz, who heads neuroanatomy, is now at Giessen (Hessen), as is also Hallervorden, who is

*The collection of Bombus numbers about 300,000, and that of Carabus about 100,000. The collection was amassed partly through purchase of smaller collections. One rare specimen cost them 400 gold marks. Many new species were discovered by the Vogts. Some of the new species of Carabus described by their associate D. Beheim-Schwarzbach were given the following names: Apotomopterus vogtae (from Siam), Eucarabus vogti (from Korea), Eucarabus vogtianus (from Korea), and Eucarabus céciliae (from China).

in charge of neuropathology. The neurosurgical department, headed by Tönnis, is soon to be moved from Bochum to Cologne. The department of Kornmüller is in Göttingen, and that of Patzig in Marburg.

Since 1945 the Institute at Berlin-Buch, renamed the Institut für Medizin und Biologie, has been in the Russian zone. It now houses a number of departments concerned with problems of cancer. When Spatz left Berlin in 1945, the gifted Timoféeff-Ressovsky, chief of the department of genetics, insisted on staying behind. His subsequent fate and that of some of the other workers who remained in Berlin-Buch is still not entirely known.

FIG. 6. The Institut für Hirnforschung und allgemeine Biologie in Neustadt.

The Vogts reached their wooded retreat near Neustadt some 14 years ago. It was not long until the grounds around the institute were planted with trees of their choosing, including many rare conifers. Their purchase of these trees was their one luxury. The summers found them searching for new races of bumblebees on which to continue their study of geographic variation, and in the winters, when the snow lay deep, they concerned themselves with the many birds in the region, seeing to it that they had sanctuary and food.

In due time the institute took form and flourished.[70] The Vogts missed their associations in Berlin, but found in the quietude of the Schwarzwald a rare opportunity to work undisturbed. The personnel now numbers about 17, of which eight are members of the professional staff. Their daughter Marguerite was with them as geneticist from 1940 to 1950, but now is in Pasadena, California, pursuing the same work.

The institute in Neustadt now houses serial sections of well over 500 brains. Cases of extrapyramidal motor disorders, numbering about 130, have perhaps the best representation. Included is the collection of Hugo Carl Liepmann (1863-1925), which is only natural, for the Vogts performed all the neuropathologic work on Liepmann's cases, and thus founded the pathologic anatomy of apraxia. The institute also possesses the electroencephalographic collection of Hans Berger (1873-1941), donated to the Vogts by Berger when he retired from his university position. Also to be found in the Vogt collection are the brains of many distinguished persons, including those of the pathologist Aschoff, the neuroanatomist A. Forel, the chemist Ostwald, the poet Sudermann, the musician Ysaye, the anatomist Fick, the sociologist Tönnies, the linguist Krebs, the psychiatrist Sommer and the Swedish neurologist S. E. Henschen.

The Vogts' method of preparing serial sections of the brain, perfected over a period of 50 years, is of considerable interest. After about two weeks' fixation in 10 per cent formalin, the cerebellum and brain stem are removed from the cerebrum by a transverse incision through the upper pons. The cerebrum is then cut coronally into four or five blocks and then sectioned in the midline, making, in all, eight or ten blocks. These are run through the alcohol series and then embedded in paraffin. Sections from blocks which have thus been embedded for as long as 20 years will stain as well with cresyl violet as those recently embedded. Most of the sections are cut at 20 microns, some at 10 microns.

When the new institute at Neustadt had been put into running order, the Vogts' lives resumed their previous tempo, which was as regular as clockwork. They have continued to rise at 8:00, and at 9:00 were to be found at their microscopes or poring over an uncompleted manuscript. From 12:30 to 1:15 there was lunch, followed by a siesta. When guests were present they, too, were each assigned a sofa until called for coffee at 2:30. After that, work was again resumed. At 7:30 sharp they sat down to dinner. Afterwards the evening was passed in conversation or in catching up on the political news. In recent years they have retired early.

The Vogts' adherence to a strict routine was the result of a decision made in the Berlin-Buch days that their hours must be spent judiciously if they were to continue their research and at the same time enjoy with their friends the amenities of life. The intense work sometimes made dispositions suffer, and Oskar Vogt's polemics with distinguished colleagues at open meetings, when tempers flared, were a sure means of sharpening wits and inciting further investigation. He gave no quarter where he believed a principle to be involved.

As guest of the Vogts for a month in early 1951, the writer soon realized that Oskar Vogt was a man with "eine starke Natur." He had an appearance which gave one an impression of extraordinary strength, a strength which matched his determination; he was rather short, his head was set on a deep and massive chest, his trunk was broad, and his arms long and dangling. He was, in turn, irascible and most engaging. Above all he was deeply earnest. Demanding a certain perfection in his associates,

FIG. 7. (*Top*) Professor Staudinger, of Freiburg i/Br., congratulates the Vogts on the commencement of their jubilee year, April 6, 1950.

FIG. 8. (*Below*) Oskar Vogt expresses appreciation for the jubilee party in honor of his 80th birthday. The others are: Professor O. Köhler (zoologist), and on the extreme right, Professor F. Büchner (pathologist); both are of Freiburg i/Br.

he laid himself open to animosities. He was impatient with delay and indirectness, and when confronted with either, his countenance would quickly gather storm clouds and then his voice would thunder. Some of those around him developed the habit of saying "ein Augenblick, bitte" in response to a request made by him, even when no storm was in sight. His voice was vibrant, slightly metallic, always authoritative, and even in ordinary conversation had such penetrating power that it would have served him well had he been a pirate like his ancient ancestor. His speech was always direct, to the point, never urging, never beseeching, never ironic; he said what he meant and he said it convincingly; he never resorted to the subterfuges of an actor. Reverses caused him to become angry, not submissive. He was not one to speak niceties for politeness' sake: the story goes that when a former associate with whom he had had some differences dropped in to wish him a happy birthday, Oskar Vogt barked, "Your greetings are accepted," and then turned and walked off. But all this was only a part of the man. He had a fine sense of humor. With

friends he was outgoing and an excellent raconteur. There was a gentleness about him when he fondled his flowers or fed his birds. For visitors he had endless patience and gave no thought to time as he demonstrated lantern slides and photographs illustrating his studies or gave himself over to their other interests. In such sessions Oskar Vogt was at his best, for one could always extract from him a wealth of new and original ideas.

Without Cécile, Oskar Vogt's achievements would necessarily have been of lesser magnitude. She, too, had ideas and imagination, and perseverence and a gift for accurate observation. Only last January, Oskar Vogt was heard to remark: "Es ist wunderbar wenn mein Frau durch des Mikroscop sieht, findet Sie immer etwas Neues."* There was delightful French objectivity about her. She was the soul of equanimity. She had a happy, independent and free spirit which was never ruffled. When she differed with some one, she spoke out in her customarily soft voice with an assurance based on rich experience which left little room for argument. In rambunctiousness among her associates she saw the humorous side. Over her wine and Swiss cheese at the end of a meal she was a match for her husband in repartee. She was endowed with an endless patience, and rarer still, the faculty of pleasing others. One soon learned not to be surprised to find her, at her 75 years, down on the floor on her hands and knees before a cabinet of slides, seeking out a certain slide in the lowermost tray, for which someone or other has asked her. Personal aggrandizement was not a part of her nature. After the Vogts moved to Neustadt she had less time for scientific work for she had to turn her attention to practical matters. She took on the administrative duties of the institute and provided the staff with the necessary specimens and accoutrement. She did the secretarial work for her husband and even typed his manuscripts. On top of this she managed the household, frequented by guests who came and went at such odd hours that she would have to go running through the institute to count them to know how many places to set at the table.

With the turn of events some years ago, the Vogts' financial means steadily shrank to an alarming degree. The Vogts and their pupils have managed, nevertheless, to publish work after work, all of the same high calibre as previously. Some have been on the theme of aging of the brain, for instance, the significance of the Nissl substance and the life history of the nucleolus. They have also continued to study the structure of the thalamus and the pathology of progressive chorea. More recently they have reinvestigated the pathology of schizophrenia and have presented

*It is marvelous when my wife looks through a microscope for she always finds something new.

evidence contrary to the general opinion that the findings in this elusive disorder are "negative." But perhaps the most significant of them all has been the study of the structural peculiarities in the brains of those who were specially gifted or delinquent. Such studies had previously been performed, but only from the standpoint of gross features; the Vogts' approach was both gross and cytoarchitectural.[42] In a man who spoke some 60 languages fluently (Krebs who was attached to the embassy in Berlin), the temporal lobe was greatly overdeveloped; in a talented violinist (Ysaye of Belgium) there was an extraordinarily high degree of development of the transverse gyri of Heschl and of other parts of the ventral lip of the Sylvian fissure; in a person of remarkable intellect who was so lacking in visual appreciation that he could hardly find his way home, a 50 per cent reduction in the area striata was found; and in two impulsive murderers the IIId lamina, said to be concerned with associative function, was strikingly underdeveloped. Always when one part of the brain was exceptionally well developed, other parts were in the realm of normal or they were underdeveloped; hence, universal genius was considered impossible. This sort of work, only in its incipiency, will have great sociologic importance if control studies bear out the Vogts' contentions.

Cécile and Oskar Vogt's most recent article, "Importance of neuroanatomy in the field of neuropathology," appears in the present issue of this journal. In it they draw from their rich experience of the past and point the way in which future investigations of the nervous system may, with great profit, be pursued.

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# Importance of Neuroanatomy in the Field of Neuropathology

*Cécile and Oskar Vogt*

THE purpose of this paper is to discuss the role played by neuroanatomy in increasing our understanding of neuropathologic processes, and in doing so, to present certain previously unpublished observations.

## CONCEPT OF BIOLOGY AS IT RELATES TO NEUROPATHOLOGY

The aims of our studies in the field of pathology and the procedures employed have been strongly influenced by our concept of biology.[41] In our view, psychologic phenomena are an integral part of the manifestations of life. Thus any investigation of these manifestations must be conducted with attention both to material processes, which are dealt with in physical biology, and to the phenomena of consciousness, with which psychology is concerned.

Chemical studies, particularly those on macromolecules,[27] indicate that the transformations a molecule may undergo do not depend solely on the atoms which compose it and the total energy it contains, but also on the configuration of the molecule and details of its structure. From such observations it may be concluded that the material processes of life are the sum of changes not only in substance and energy but also in structure. The changes in substance and energy are the subject matter of physiology, and alterations in structure are in the province of morphology. Every material process of life has a morphologic aspect which consists of some alteration of a given external configuration and internal structure. Such alterations may be of two kinds: short, usually reversible, functional, or metabolic, and prolonged "phenogenetic"* ones. Among the latter we distinguish irreversible "transformations" from reversible transient "interformations." If the structures and their alterations are visible to the naked eye or to the microscope, they are in the realm of

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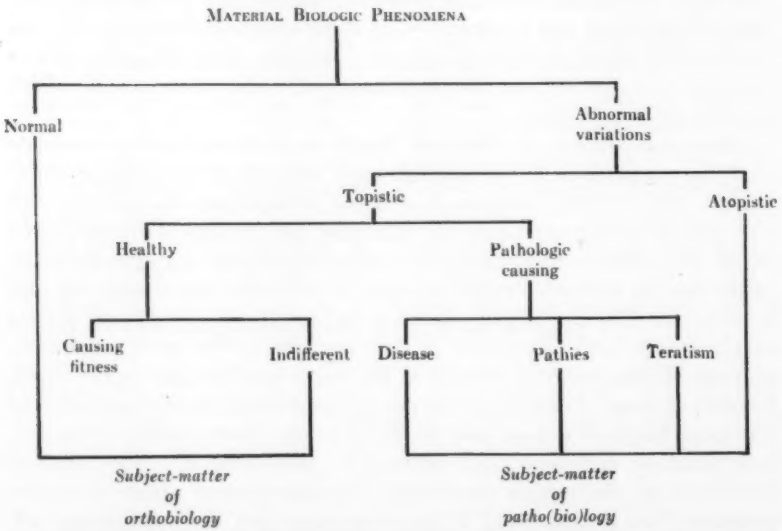
anatomy; otherwise they constitute submicroscopic morphology. The functional role of each process of life, that is, its importance for the form, survival, and activity of the individual, constitutes the subject of a special biologic discipline because it includes both physiologic and morphologic phenomena. It may be termed ergology. Physiology and morphology, it may be reiterated, are concerned with the *nature* of biologic phenomena, ergology with the *value*, or significance, of all biologic processes in the life of the individual.

A few introductory words concerning our classification of pathologic phenomena are also in order. There are damaging agents, such as vascular disease or trauma, the effects of which are crude and mechanical and injure all components of a tissue indiscriminately. Contrasted with these are other noxious agents, the action of which is confined to certain tissue elements, thus causing what is referred to as systemic lesions. Inasmuch as the term "topistic" has been adopted for the discipline concerned with the systemic units of the organism, systemic lesions are also topistic lesions. On the other hand, those lesions caused by crude mechanical

FIG. 1




*E. Haeckel[12] used the term "ontogeny" to refer to the changes in an individual throughout its lifetime. However, this term is now employed to designate only the changes that take place up to maturity. To cover the entire life span of an individual (i.e. the changes up to maturity as well as in adult life and in involution) we suggested use of the term "phenogeny." This term thus refers to all the changes which the phenotype may incur.[43]

trauma are "atopistic." We have been able to show that normal variations and pathologic variations (i.e. topistic lesions) are of the same quality but differ in intensity. Because of their intensity, topistic lesions interfere with the balanced behavior of the average individual and thus acquire a pathologic character.[39] They may be subdivided into 1) diseases with clinical signs, 2) "pathies," in which clinical signs are absent because of compensatory functions of other tissues, and 3) permanent nonprogressive deformities. The normal material manifestations of life and normal variations are the subject matter of so-called orthobiology (Aschoff), while the pathologic variations and atopistic lesions are the concern of pathobiology, or pathology (figure 1).

CYTOARCHITECTURAL UNITS AS SUBSERVING DIFFERENT FUNCTIONS

In the last decades of the nineteenth century, steady progress was made in the discovery of the anatomic nature of phenogenetic cerebral alterations. Around the turn of the century, we undertook neuroanatomic investigations in the hope of throwing additional light on the origin of clinical signs and symptoms. We also hoped to be able to extend these investigations to include normal cerebral processes, and possibly to detect ways and means of influencing beneficially, or of preventing, some incurable nervous diseases by pharmacologic methods.

Our investigations have been based entirely on a study of serial sections of the brain. Such sections are requisite if any degree of success is to be achieved in neuropathology. The brains were embedded in paraffin and a procedure used which makes it possible to stain and destain each section repeatedly.

In sections of normal adult human brains stained with cresyl violet (Nissl's method), hundreds of different kinds of nerve cells can be distinguished, many more even than Ramón y Cajal was able to detect with his silver method. They differ in size and shape, in the number and shape of the Nissl bodies, in the occurrence within the cytoplasm of other characteristic substances, in the development and position of a lipophil center ("spongioplasma") or of a clear center. There are differences also in those parts of the dendrites which are stained by this method, i.e. the proximal parts. Differences are in the number and the caliber of the dendrites, their site of origin, their manner of branching and their content of Nissl substance. Furthermore, there are variations in size, shape and position of the nucleus, in the contour of its membrane, in the properties and shape of the chromatin within the nuclear membrane itself as well as inside and outside of that membrane. The properties and shape of the chromatin in the nuclear protoplasm may vary, and so may the number of nucleoli, their size, chromatin content, and vacuolization, and the number, size and shape of the nucleolar marginal bodies.

The nerve cells of each type are limited to a particular region of the gray matter, where they may be associated with other types or constitute the only cell type. Such a region, characterized by one or several cell types and by the number of nerve cells and their distribution, is called a *griseum*. A griseum not only has a particular cytoarchitecture, but is also characterized by differences in caliber, number and arrangement of myelinated nerve fibres (myeloarchitecture), by differences in the properties of the glia (glia-architecture), and frequently by pecularities in the blood vessels (angioarchitecture). Where grisea occur in layers, they are called *laminae*. In every part of the cerebral cortex we meet with a characteristic combination of laminae of specific structure. The combination persists for a certain distance until new combinations occur at its boundaries, usually in such manner that even each lamina of the new pattern is different. A cortical field of uniform structure is called an *area*. It may be emphasized that a cortical area is a highly developed griseum composed of a number of laminae, each of which is an *elementary griseum*. The grisea in the basal regions of the brain and in the brain stem are referred to as *nuclei*.

In the cerebral cortex combinations of these different cell types form about 200 areas. The thalamus is composed of many more nuclei than have hitherto been identified—approximately 150[16, 33]—and the same may be said of the hypothalamus, which, according to Brockhaus, contains about 55 nuclei and subnuclei.[4]

With the discovery of the great number of structural units in the gray matter, the question arose whether a different function could be assigned to each griseum or to a combination of a few grisea as represented by the different laminae within a single cortical area. We have worked on this problem since 1903.

A number of functional tests applied to different grisea in man and in animals have shown that no two of these regions are identical in function. These tests include the reactions of the griseum to electrical stimuli and recordings of its action currents and the functional deficiencies arising from naturally occurring (atopistic) or experimental destruction of parts of the brain, and relating these phenomena with the study of fiber connections of particular cell types. Because of advances in comparative anatomy, it has become possible to apply to man certain functional information obtained from animal study.

During recent decades two methods have enabled us to gain further knowledge concerning the function of topistic units. First, it has been found that certain healthy, but exceptional, individuals who were endowed with an unusually low or high degree of some cerebral functions

had certain architectonic units correspondingly underdeveloped or overdeveloped.[43] Second, it has been possible to correlate clinical syndromes with underdevelopment or disease of certain grisea.

Thus, from the observations of other workers as well as from our own experience, the conclusion has been reached that architectonic division of the gray matter is, in fact, also a functional division.

### IMPORTANCE OF CYTOARCHITECTONICS AND MYELOARCHITECTONICS; CONCEPT OF PATHOCLISIS

As a result of this last conclusion, the architectonic subdivision of the cortex and the tracing of fiber connections between the nerve cells of different types become matters of paramount importance in neuropathology. Fields of study in which the essential nature of this knowledge is clearly seen are many and significant.

1. The aggregation of representatives of a particular cell type into grisea is of great methodologic value, since it facilitates recognition of the members of the same cell type and investigation of all the alterations a single type can undergo.

2. The existence of separate grisea implies separate function and stimulates the search for that function.

3. The different structure displayed by neighboring grisea indicates that their functional difference results not only from the different afferent and efferent fibers they possess, but also from the intrinsic differences in the structure of their nerve cells. This view of cortical function is contrary to that held in the nineteenth century.

4. We would expect that changes in the cellular structure would lead to alterations of function. The usefulness of that conclusion will depend on whether or not the *morphologic* peculiarity which we assume to exist whenever cerebral function is abnormal is of an *anatomic* nature. Experience has shown that it often is, for we have been able in all cases thus far examined to demonstrate anatomic peculiarities or alterations in the brains of individuals whose mental achievements were far above or below the average, in congenital or acquired idiocy, in schizophrenia[7, 40, 41, 48] and other psychoses, and, finally, in the dyskinesias. As far as our present knowledge goes, it is permissible to correlate these alterations with the degree of mental ability or with the disease process, in spite of the fact that some of these conditions had previously been considered to be functional psychoses or neuroses.

5. Most of these alterations are topistic in character. How is that possible? Just as the transformations a molecule may undergo are determined partly by its configuration, so also may the life history of a nerve

cell be influenced decisively by its anatomic differentiation. This is well illustrated in the normal ageing process of the nerve cell, for the time at which the involutionary process begins and the speed of its progress until halted by death varies from cell type to cell type. In some the ageing process may consist of simple shrinkage, in others in the replacement of normal cell constituents by clear fatty substances or by lipofuscin. This replacement starts at a different site in each type of cell and proceeds according to a different pattern. Several involutionary processes may also occur in the same cell. These processes of ageing form part of a normal involution, or *ortho-involution*, but represent a *patho-involution* if they occur abnormally early in life. We speak only of patho-involution when the histologic process is identical with that of the ortho-involution of the nerve cell type. Gowers' "abiotrophy" is not based on this definition.

The morphologic peculiarity of each cell type not only determines its normal life history, but also influences the nature of the alteration it may undergo. Each nerve cell tends to react to various influences in a certain specific manner. This disposition of the nerve cell is called its *clisis*. If this predisposition leads to the development of normal variations, we are dealing with the phenomenon of *orthoclisis*, and if the results are pathologic, then with *pathoclisis*.

The tendency to undergo a specific reaction (i.e. clisis) is also a characteristic of the glia. Normally, the striatum (caudate nucleus and putamen) is poor in fibrous glia, the dentatum (nucleus dentatus of the cerebellum) rich. If, as in Wilson's disease, both putamen and dentatum are seriously affected, the fibrous glia in the dentatum are enormously increased, whereas these cells in the putamen are increased very slightly or not at all.[26]

The blood vessels of certain grisea also demonstrate the phenomenon of pathoclisis. Five cases have now been reported[3, 18, 20] in which a deposit of pseudocalcium in blood vessel walls caused an angiopathy restricted to laminae IVc and IVb$\beta$ of the area striata of the occipital cortex. There is, moreover, the tendency of the blood vessels of the striatum to exhibit "dyshoric"* processes, i.e. an increased permeability for blood plasma and its proteolytic enzymes, the latter acting to destroy tissue. In the adult, the passage of larger amounts of plasma through the walls of these blood vessels causes progressive chorea. In the newborn, it produces the condition known as *status marmoratus*,[28] reflected clinically by athetosis. Smaller, similar plasma transudates in the aged cause what Pierre Marie[19]

*Dys*: poor; *horos*: barrier. The word "dyshory," formed by Schürmann, is used in connection with the permeability of larger molecules and hence, in contrast to the process of edema, the extent of the lesion is limited.

called *vaginalite destructive* and lead to Durand-Fardel's[9] *status cribratus* and our[30] *status praecribratus.* According to Dowse,[8] Hassler,[13-15] and ourselves[30] this condition, which may be hereditary, occurs most readily in the striatum and causes tremor.

6. Every disease that arises as the result of pathoclisis is topistic by nature. The histologic picture of such diseases varies greatly depending on the nature of the disorder, whether metabolic, inflammatory, etc., and the differences in the picture elucidate many details of pathoclisis.

a. In our material, we have not encountered a single brain in which disease was confined to one griseum. Discounting retrograde and transneuronal cell lesions, the morbid process was found either in a few or in many places (pleiotopic or polytopic localization). This multiple localization indicates that different grisea possess a similar pathoclisis towards the same noxious agent. However, though the pathoclisis of different grisea may be similar, it is usually not identical. As a rule, in such a group of grisea with similar reactions the pathologic process commences in each at a different time and proceeds at a different rate of speed. Frequently these differences in timing are consistent, and the susceptibilities of the group of grisea may therefore be graded according to a fixed order. This phenomenon we call *eunomy.*[29, 31]

An instance of unequal pathoclisis of cortical layers is that due to extravasation of plasma through the wall of a blood vessel. Let us consider that main part of the cortex which has seven layers, the so-called isocortex, and measure the distance from the vessel wall to which cell destruction proceeds. This distance is greatest in lamina III and decreases in the order III, V, II, VI and VII, IV. This is a eunomic order. The whole process is complete in a few hours so that retrograde or transneuronal lesions are excluded from consideration.[34]

In amaurotic idiocy, the one disorder in which all nerve cells are affected, different degrees of pathoclisis manifest themselves by the different speeds at which the cells disappear. Thus, the granular cells of the cerebellar hemispheres have already succumbed at a time when those of the vermis and flocculus still are present. The next stage is a disappearance of granular cells in the center of the vermis.[11] Here, again, is an instance of eunomy.

b. In a griseum which contains only one type of cell (an isomorphous griseum according to Kohnstamm[17]), all cells do not succumb to the disease simultaneously. Frequently the first cells to be affected lie together in groups. Lesions characterized by initial spotty cell involvement followed later by general cell destruction are referred to as holotopistic.[34]

In senile dementia it frequently happens that the nucleus centralis thalami (centre-médian of Luys) has lost all but a few remnants of nerve cells, whereas none of the surrounding thalamic nuclei has lost cells.[33, 34]

If cells of several types are present in one griseum, a pathologic process may affect one type only. The nuclei tuberis laterales of the hypothala-

mus, for instance, contain many small cells. They also include isolated large nerve cells of the type common in the nucleus tuberomamillaris. In the one form of chorea which we consider to be the genuine chorea of Huntington, all the small cells of these nuclei may have disappeared while the isolated large cells have remained intact.[46]

In some instances the morbid process appears to be confined at first to a part of a griseum. It is then called a "merotopistic* process." We speak of an atopistic process in a particular part of the brain only when adjacent parts, similarly exposed to a noxious agent, are unaffected. The term "merotopistic alterations" has the connotation that the non-damaged part of the griseum is exposed to the same noxious agent. There must be a biologic difference between the damaged and undamaged part of the griseum: that is our theory.

Apparent examples of the merotopistic process were found in two cases of amaurotic idiocy.[24, 34] Both brains showed lesions in the cornu ammonis. The damage was, however, not located in the usually very susceptible field $h^1$ (Sommer's sector), but in part of the more resistant field $h^2$. Further investigation of field $h^2$ revealed that it consists of two parts which differ in their structure and are now named $h^{2a}$ and $h^{2b}$, and that the diseased part had the outlines of $h^{2b}$. Thus a disease which at first sight appeared merotopistic, proved to be holotopistic when our architectonic knowledge had sufficiently progressed. These observations have been confirmed by the discovery of two instances in which a morbid cell condition was found clearly restricted to field $h^{2a}$. One was a case of Pick's disease and the other schizophrenia with terminal pellagra.[34]

The black zone of the substantia nigra (called by us "subnucleus niger compactus") consists of a number of fairly well separated cell clusters. Of the 14 clusters lying in the caudal part of that subnucleus, Hassler[14] found that only four (which are adjacent to each other) tended to show lesions, and that these lesions usually occurred in a particular order. Thus far, however, it has not been possible to discover structural differences between these four susceptible cell clusters and the resistant ones. Nonetheless, we do not doubt that this merotopistic process will one day be given a morphologic basis.

"Topistophilic" processes are those in which vascular lesions causing destruction of the parenchyma are restricted more or less exclusively to certain grisea. The dyshoric processes of the striatum discussed in the foregoing belong to this group.

Finally, we speak of "topistoid" processes when parts of adjacent grisea show lesions of different severity in response to a single noxious agent. An example is the different degree of resistance of the cortical laminae to a circumscribed transudation of plasma. When the alterations are of the same kind but of different degree we have a eunomy. In the beginning of a topistoid process only one griseum may be damaged.

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*meros: part; topistic: a topistic unit, or griseum.

c. The phenomenon of pathoclisis may be classified not only with respect to topistic localization of the morbid process, but also according to the different degree of tissue susceptibility and the type of histologic response elicited. Certain grisea are susceptible to particular noxious agents. We call this their special pathoclisis and contrast it with general pathoclisis. The latter is a susceptibility to many damaging agents and may be considered as a summation of several special pathoclises. If the result of the tissue reaction is a peculiar or unique histologic process, the underlying pathoclisis is called specific. If the reaction is only quantitatively different from that of other nerve cells or that due to other damaging agents, the underlying tendency is referred to as nonspecific.

In the cornu ammonis, lesions in field $h^1$ may occur in vascular diseases, avitaminoses, senile dementia, Pick's disease and general paralysis. This is an example of general pathoclisis. Another example is the susceptibility to many noxious agents of lamina III of the isocortex. In contradistinction to the marked reactivity of field $h^1$, lesions in field $h^{2b}$ occur, as far as we know, exclusively in cases of amaurotic idiocy. Field $h^{2b}$ thus shows a special pathoclisis. This does not prevent the histologic lesion in that field from being one of the ubiquitous alterations characteristic of amaurotic idiocy. In other words, the pathoclisis of $h^{2b}$ is nonspecific. In contrast, the total necrosis of the striatum in Wilson's disease and of the pallidum in carbon monoxide poisoning represent specific processes. They are based on a specific pathoclisis of these nuclei, which is one of their many susceptibilities, the sum of which constitutes their general pathoclisis. Of the two nuclei, the striatum is the more vulnerable.

### ETIOLOGIC CLASSIFICATION
### BASED ON PECULIARITIES OF HISTOLOGIC LESIONS

The very high vulnerability of the striatum makes it particularly suited to the elucidation of some fundamental questions in neuropathology.

We have examined more than 40 cases of progressive bilateral chorea and they all showed histologic lesions in the striatum.[42] These varied so greatly that we were able to distinguish eight different types:

1. Encephalitic processes: a) lesions characteristic of general paralysis, and b) lesions of a nonsyphilitic nature (3 cases and 1 case, respectively).

2. Crude dyshoric lesions of varied etiology (4 cases).

3. Edema: a) primary, following vascular damage by murine typhus (1 case), b) of unknown etiology (1 case), c) in hereditary chorea precipitated by a renal abscess (1 case), d) in the final stage of Huntington's chorea (1 case).

4. Huntington's chorea. In addition to diffuse, severe loss of nerve cells, particularly small cells, there is always great proliferation of the macroglia and the oligodendroglia. Heredity often was proved (15 cases).

5. Shrinkage of nerve cells of the striatum with little depletion in number. In places there is a moderate degree of glia proliferation. The nerve cells of the nucleus centralis thalami, however, have vanished. Hereditary. This is de Brux's[5] "chorée striopète" (1 case).

6. Dwarfism of the nerve cells.[32] Hereditary (2 cases).

7. Special localization of senile dementia (1 case).

8. No loss of cells in the striatum, but most of them were damaged, and as a result were transformed into so-called wasting cells, or "Schwundzellen," i.e. their cytoplasm became progressively vacuolated and then disappeared whereas their nucleus remained relatively unaltered. Probably a form of schizophrenia (1 case).

Nearly all cases listed under numbers 1 to 7 were diagnosed during life as Huntington's chorea. Nevertheless, not only did we find different histologic processes underlying the chorea, but also hints pointing to the etiology of these histologic processes and thus to the basis of their future etiologic classification.

It happens that a specific lesion occurs only in very few cells. In a study of the nucleus coeruleus in 12 cases of postencephalitic parkinsonism, Beheim-Schwarzbach[2] found in every instance that cells had undergone Alzheimer's fibrillary change; in none of them, however, did the cytoplasm show Masson-staining vacuoles. The reverse was true of 14 cases of paralysis agitans; some cells contained Masson-staining vacuoles, but none displayed Alzheimer's fibrillary change.

The etiologic classification may be supported by a second group of observations. It has been stated in the foregoing that all topistic brain diseases we have studied have been characterized by multiple lesions. These vary with the etiology, a fact of particular importance when dealing with hereditary diseases. It is known that different mutations may cause certain identical physical manifestations. In man, therefore, we cannot decide whether two families with similar clinical signs carry the same mutation. Apart from differences in the histologic picture, a different multiple localization may help in answering that question.

The nuclei tuberis laterales of the hypothalamus were normal in group 6 of the preceding classification of chorea. Wahren[45] has shown in the other seven groups, however, that these nuclei suffered cell loss. On the other hand, group 6 showed peculiar histologic lesions in the dentatum and in the anterior thalamic nucleus. Furthermore, Weisschedel[47] observed destruction of cells in the superior olivary nucleus of certain patients with chorea. This lesion was absent in the groups 1b, 2, 7 and 8,[46] and was present in all the others. In group 6, concerning mother and son, only the son, who fell ill earlier in life than his mother, had a lesion in the superior olivary nucleus.[47] That lesion was, however, not the same histologically as that seen in other cases of chorea.[46]

Thus we are enabled to utilize differences in polytopic manifestations for the etiologic classification of chorea. Gradually we shall learn to recognize a group to which a case of chorea belongs from the special form the disease assumes and from its different ancillary signs. We are, in fact, already able to localize a lesion of the dentatum by means of cerebellar signs, and to recognize lesions of the anterior thalamic nucleus by early disturbances of micturition and defecation.

## TASKS FOR THE FUTURE

In the foregoing pages we have briefly reported some of our basic observations. How far have they fulfilled our expectations or at least given us hope for the future? Altogether they constitute only the beginning of an accumulation of knowledge that we anticipate for the future, but enough to assure us that the hopes with which we started a lifetime's work have not been false hopes.

A number of clinical signs and symptoms now exist which make it possible to determine exact localization. Further well defined localization of functional disturbances of a topistic nature will gradually allow more precise understanding of the normal function of the affected grisea, though, in that field, extreme care in drawing conclusions will be required. We wish particularly to emphasize the possibility of finding an etiologic classification of cerebral diseases by means of neuroanatomic investigations.

We know that in development each gene produces a special enzyme and that this enzyme takes part in the transformation of certain substances. At a given time the enzyme is present in a certain concentration at a particular site where it is required for the harmonious development of the organism. Mutations may interfere with the production of these substances. In experimental genetics, it has been demonstrated that such interference may be prevented through replacement therapy. It should be our aim to try to carry out such substitution therapy in congenital disease in man. Such enzymes and the substances transformed by them are present in normal grisea, but are absent in identical grisea when they have undergone congenital pathologic changes. The first step in the prevention of the manifestations of pathologic genes is the identification of the site of the lesion; in nervous disease, the affected grisea. The next step would be to extract from normal tissue the substance lacking in affected tissue. If this step were achieved, the task then would be to enable, on the basis of etiologic classification, a selection of those individuals whose progeny could be protected from the manifestation of their pathologic constitution by replacement of the needed substance.

Finally, we should like to draw attention to three more results obtained in the course of our investigations.

1. Anatomic observations have led us to believe that transneuronal degenerations in old people are to be considered evidence of premature ageing. Our inference from this, which is of no small social importance, is that activity retards the ageing of nerve cells.[35, 36]

2. Other observations have increased our knowledge of the means by which the nucleus carries out its work of cellular repair.[21, 36-39, 43] This has stimulated the search for substances which enhance this activity of the nucleus.

3. As early as 1910 we[44] pointed out that the architectonic areas varied in their topographic relations to the sulci. O. Vogt's myeloarchitectonic field 56, for instance, usually lies rostral to the ventral part of the gyrus centralis anterior, but it may also lie on the surface of that gyrus. The variability in the reactions which Penfield[22] obtained in his numerous electrical stimulations of the human gyrus centralis anterior may be due to such architectonic differences in the central gyrus of different individuals. Schaltenbrand[23] has recently stated that in the single individual functional localization is precise, but that it varies between different individuals so that localization is only of statistical importance. Our comment is that the main reason for these variations lies in the inconstancy of the relations between areas and gyri: the former are consistently related to one another, but their positions vary individually with respect to the gyri. In the first description of myeloarchitectonic fields, Elliot Smith[25] had already emphasized that sulci should not be considered homologous unless their walls were shown to consist of identical architectonic areas.

From the foregoing review we draw the conclusion that advances in neuropathology resulting from neuroanatomic research are not a matter for the past but for the future.

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• And it is gratifying to perceive that the functions of the brain and nerves are now attracting the attention of medical inquirers, much more than at any former period. Many of the most industrious and distinguished members of the medical profession, and such as from official station and other advantages have the best opportunities for investigating such subjects, are prosecuting inquiries with great earnestness respecting the growth, structure, and diseased appearance of the brain and nerves, with a view of ascertaining their functions and remedying their diseases. We may therefore reasonably expect within a short period valuable additions to our knowledge of the nervous system. We are encouraged in this belief from the important facts which have been made known within a few years by the labors of Gall, Reil, Spurzheim, Flourens, Bell, Magendie, Foville, Lallemand, Abercrombie, Andral, Serres, Tenneman, Muller, Hall, Solly, Grainger, etc., who, with many others, have cultivated this department of medical inquiry. These distinguished men have not pursued the same methods of investigation; some have had recourse to experiments upon the living nervous system; others have chiefly devoted their attention to its diseased condition and to noticing the symptoms produced by this condition; while others have watched its growth and development, and marked the manifestation of function at different periods; and from these dis-similar methods of investigation, we have within a few years been put in possession of more knowledge respecting the nervous system, than had come down to us from all previous time.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

# Succinate Therapy in Multiple Sclerosis

*Robert B. Aird, M.D.*

THE hazards of clinical research become excessive in dealing with the treatment of multiple sclerosis. S. A. Kinnier Wilson[1] has expressed this well in stating, "Causal ignorance entails an unfortunate diffusion of therapeutic endeavour, and spontaneous remissions make it difficult to assess the value of any particular treatment. The pharmacopeia has been ransacked for 'nerve tonics' which flatter only to deceive." Correspondingly, in reporting a study dealing with the treatment of multiple sclerosis, it is essential that it be presented in proper perspective. Reviews[2] of current therapy in multiple sclerosis emphasize the pitfalls of evaluating empirical therapy in this elusive condition, which is characterized not only by spontaneous remissions as mentioned by Wilson, but also by a mood or euphoria which makes the multiple sclerotic patient unusually responsive to psychotherapeutic suggestion.

It is of considerable interest that those methods which presumably have served to improve vascular supply have been observed by many workers to be of some benefit in multiple sclerosis. The evidence, however, does not permit deductions as to whether the benefit is the result of improved tissue oxygenation, or an improved vascular supply in other respects. Again it is not clear, although it seems likely, that such beneficial effects are concerned with physiological factors of secondary importance in the acute stages of the disease rather than mechanisms of primary, etiologic importance in multiple sclerosis. Regardless of these considerations, the systematic trial of mechanisms which may improve tissue oxygenation in the central nervous system has seemed well justified.

Numerous studies[3] have demonstrated the important role of succinates in biologic oxidation, and they have been found to stimulate cellular respiration.[4] Succinic acid has been shown to act as a catalyst in the

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Krebs cycle in the metabolism of carbohydrates[5] and fatty acids,[6] and is also involved in the oxidation reduction of cytochrome.[7] In addition, it has been demonstrated that the use of succinates may prevent the inactivation of succinic dehydrogenese by oxidized glutathione and inhibitors that react with the sulfydryl group of the enzyme.[8] It has also been shown that succinates increase the synthesis of acetylcholine.[9] Based on the observations of Quastel and Wheatley,[10] numerous studies have been devoted to the use of succinates as analeptics for barbiturate poisoning.[11] Large doses of this agent have been used intravenously with little or no toxic effect and have produced a rather remarkable resuscitation in some patients. The effect is thought to be an enzymatic one concerned with the more efficient utilization of oxygen by the tissues and, in the case of barbiturate poisoning, presumably supplies a substrate aiding cerebral oxygenation processes which are not materially affected by the barbiturates. Since sodium succinate can be taken safely in relatively large oral doses and is readily available and reasonable in price, it was selected for trial.

## METHODS OF STUDY

### *Intravenous Sodium Succinate*

Twenty milliliters of a 30 per cent solution of sodium succinate has been given slowly by vein with the patient in a recumbent position. The initial 4 or 5 ml. may be injected at the rate of 1 ml. per second, following which the injection is made at a slower rate. The patient usually coughs within 10 or 15 seconds and a crimson flush appears in the blush areas within one-half to one and a half minutes after the injection has been started.

At 5, 15 and 30 minute intervals after the injection, the patient is carefully examined with special attention to those points which have been found to be abnormal in the initial neurologic examination. A careful initial examination is of primary importance, of course, if one is to establish a base line for comparison. Although notes are made on the patient's subjective reactions to the test, the attention of the examiner has been directed principally toward eliciting objective evidence that might establish whether or not the patient's condition was altered and benefited by the injection.

Intravenous administration of sodium succinate has been done as an initial pilot procedure for the subsequent oral administration of this agent. Another reason for doing the intravenous test was to establish on an objective basis the type and degree of benefit occurring from the succinate. The fluctuation of signs and symptoms in multiple sclerosis makes it difficult to evaluate changes with any degree of certainty. Objective

changes observed within minutes, however, can scarcely be explained on any basis, except as physiological changes produced by the injection.

*Oral Sodium Succinate*

This has been started with a level teaspoonful (4.5 to 5 gm.) of sodium succinate powder in an ounce of water, three times per day. If this is swallowed quickly and followed by tomato juice, it is tolerated very well in a high percentage of patients. If this dose produces no ill effects within two days, the dose may be doubled, that is, two level teaspoonfuls, three times a day.

Follow-up neurologic examinations have been made a few days after the full dose of sodium succinate has been established, and again at convenient weekly or monthly intervals thereafter, depending upon the course in each case.

The object of the oral succinate has been to obtain a sustained effect by a simple method which would be practical for the patient on a continuing day to day basis.

## RESULTS

The effect of intravenous succinate in 10 patients is summarized in table 1. In only one instance did intravenous succinate appear toxic. After 6 ml. were injected, this patient exhibited marked flushing and a urticarial rash began to develop. The injection was discontinued after 9 ml. were injected. Although the flush and rash persisted for about an hour in this case, no other ill effects developed.

TABLE 1
RESULTS OF INTRAVENOUS SODIUM SUCCINATE (20 ML. 30% SOLUTION) IN TEN PATIENTS

| *Improvement* | *None* | *Slight* | *Moderate* |
|---|---|---|---|
| Subjective | 2 | 5 | 3 |
| Cerebellar | 5 | 2 | 3 |
| Motor | 4 | 4 | 2 |
| Sensory | 5 | 3 | 2 |

No apparent benefit was seen in two patients and improvement in the eight other patients varied widely. Improvement in coordination was evidenced by improvement in the patients' dyssynergia, ataxia, dysmetria, balance and gait. Changes referrable to the motor system consisted essentially in an improvement in the flexor withdrawal reflex and ankle clonus. These were observed in six patients. Changes in the deep and pathologic reflexes or improvement in strength were never observed, although in a few instances the patients stated that they felt stronger. Sensory changes

consisted in subjective improvement in the appreciation of vibration and objective improvement in position sense and skin writing.

The effect of oral succinate in 25 patients is presented in table 2. Toxic effects were observed in six patients. These consisted in gastro-intestinal effects in four instances and genito-urinary effects in two others. Epigastric burning, nausea and vomiting, and in one instance possibly constipation, were reported. The genito-urinary effects consisted of increased urgency and frequency in patients already afflicted with such complaints. On the other hand, other patients with similar complaints did not develop such toxic effects. In no patients were the toxic effects alarming or dangerous. Three of these patients, in fact, were able to continue the succinate therapy with benefit on reduced doses.

TABLE 2
RESULTS OF ORAL SUCCINATE (6-10 GM. T.I.D.) IN TWENTY-TWO PATIENTS

| *Improvement* | *None* | *Slight* | *Moderate* |
|---|---|---|---|
| Subjective | 4 | 11 | 7 |
| Cerebellar | 10 | 5 | 7 |
| Motor | 12 | 6 | 4 |
| Sensory | 18 | 3 | 1 |

No effect was observed in four patients. Slight improvement appeared in 11 patients, but was verified objectively in only seven. Moderate objective improvement appeared in seven other patients. The type of improvement corresponded closely with that observed with intravenous administration of the succinate.

Deterioration of the patient's condition on discontinuation of the succinate was observed in some degree in four patients. Resumption of the treatment resulted in an improvement in all instances. Such observations have raised the question whether or not sodium succinate might be acting prophylactically to prevent remissions as well as to improve the patient's immediate condition. Although our observations are too limited to permit any conclusions in this respect, recurrences have been observed so far in only three patients who have been followed for 11, 13 and 18 months respectively on the succinate treatment.

A typical case history will serve to illustrate the changes observed with the intravenous and oral administration of sodium succinate.

### REPORT OF CASE

A man aged 29 developed clumsiness of his hands, numbness of his legs and unsteadiness of gait over a period of a few days, one and one-half years previous to treat-

ment. In addition, he noted difficulty walking in the dark, and in the daylight he had to watch his feet. A tight sensation was associated with the numbness of his legs and was felt as high as his waist. All symptoms improved within a month. The results of a lumbar puncture and myelogram were reported as normal. His symptoms continued in very slight degree over the following ten months, when he again had an exacerbation of these same symptoms, along with urinary urgency. Within a period of possibly six weeks these symptoms again improved although he continued to have some clumsiness in his hands and unsteadiness of his gait.

Neurologic examination showed the following positive findings: marked temporal pallor of the left optic disc and moderate temporal pallor on the right; slight dysdiadokokinesia bilaterally, more marked on the right; past pointing to the right with the left hand on finger to nose test; slight ataxia on heel-to-shin test bilaterally; ataxic and moderately wide-based gait; slight hypesthesia and hypalgesia bilaterally in both legs up to the knee levels posteriorly and to the middle of the thighs anteriorly; moderate impairment of position sense in hands and feet; marked impairment of stereognosis bilaterally; marked diminution of skin writing in both legs; moderate increase of deep reflexes in the left arm and in both legs.

Routine laboratory tests were normal. Gastric analysis showed no free hydrochloric acid but a moderate amount of total acid. Lumbar puncture showed initial pressure of 100 mm. of water and normal dynamics; the cerebrospinal fluid was clear, and contained 2 cells per cu. mm. and 53 mg. per cent total protein. The Pandy and serologic tests were negative and the colloidal gold curve was essentially flat.

Twenty milliliters of a 30 per cent solution of sodium succinate were injected intravenously with the usual prompt flush reaction. Five minutes following injection, the patient stated that his head felt less tight and that his hands were more nimble. Slight improvement was noted in his dysdiadokokinesis and skin writing. Fifteen minutes following the injection an improvement in gait and position sense was observed and there was some improvement in coordination. Thirty minutes after injection the patient stated that he was more dexterous with his hands and more certain of his feet. He felt that his improvement in dexterity and gait approximated 25 per cent. Objectively, it was estimated that his improvement was from 15 to 20 per cent.

The patient was discharged with the recommendation that he take sodium succinate, one level teaspoonful five times per day. Within a week the dose was adjusted to two teaspoonfuls three times a day, or a total dose of 27 gm. per day. One week following initiation of the oral succinate administration, the patient reported that he felt much better, especially from the standpoint of clumsiness of his hands and his gait. Objective examination at this time showed slight diminution in his tactile sense and skin writing. He also showed some impairment of dysdiadokokinesia and asterognosis. It was felt that his skin writing, dysdiadokokinesia and asterognosis were definitely improved over his initial examination. His position sense was now intact and his balance was considerably improved. His gait was much less ataxic than previously.

Examination three months after discharge from the hospital showed considerable subjective improvement. Neurologic examination still showed a slight asterognosis, only slight ataxia on heel to shin test and slight dyssynergia and dysmetria on finger to nose test. His position sense was estimated to be 80 per cent of normal.

## DISCUSSION

The rapid clinical fluctuations of multiple sclerosis and the remarkable

recovery which so frequently follows even initially severe episodes suggest that a high percentage of the signs and symptoms observed at the peak of an episode are manifestations of abnormal physiology rather than the result of irreversible pathologic changes. The demyelination and congestion of the plaques presumably contribute to this effect. That vasospasm may play an important role in the abnormal physiology is indicated by the benefit derived in acute episodes from the use of vasodilators and other procedures producing reflex vasodilatation. It seems likely that tissue oxygenation would be adversely affected by such factors and, therefore, that anoxia may play an important physiological role as a secondary mechanism in the acute stages of multiple sclerosis. It is also conceivable that anoxia may be a factor of some importance in the sclerosing process which predominates later in the more chronic and progressive stages of multiple sclerosis. It is this secondary physiological effect of multiple sclerosis that presumably is modified beneficially by sodium succinate. The recent observation[12] that cytochrome-C has been found in high concentration in the areas of multiple sclerotic plaques does not necessarily disprove this thesis, inasmuch as the increased concentration may reflect an increased need for oxygen rather than an increased utilization of oxygen.

As shown by the studies of Fog[13] and many others,[14] the typical pathology of multiple sclerosis is located in the lateral and dorsal columns, and usually involves only the anterior commissure in the ventral columns. Consequently, lower motor neuron lesions and muscular atrophy are infrequently observed in multiple sclerosis. Although several studies[15] have suggested that the neuropathology of multiple sclerosis follows closely the venous drainage pattern of the spinal cord, it has also been demonstrated[16] that the anterior horns and anterior columns possess an arterial supply which is considerably richer than the arterial supply to the lateral and posterior columns. It seems possible, therefore, that the pathology of multiple sclerosis may be related to the vascular supply of the spinal cord, being more marked in the lateral and dorsal columns where the vascular supply is relatively poor. On this basis, it is conceivable that tissue oxygenation might play an important role in the initial pathophysiology of multiple sclerosis. Only because succinate therapy succeeded in aborting recurrent episodes of multiple sclerosis, however, might one conclude that this was true. As indicated previously, the data of the present report are not adequate to answer this point. The progression of signs and symptoms in those patients who are affected with a steadily advancing paraplegia (sclerosis of the advanced cases) would not necessarily bear on this question nor serve to answer it.

The argument might be advanced that the vasodilatation of the intravenous succinate might be producing an effect comparable to other vasodilators which have been reported as having some beneficial effects in multiple sclerosis. Since the same type of improvement has been observed with oral succinate as with the intravenous succinate, however, and the sustained effect of the oral succinate has not been associated with observable vasodilatation, such an explanation would not appear to be tenable. A relationship, nevertheless, may exist between the beneficial effects of vasodilators and sodium succinate in multiple sclerosis. Vasodilatation is presumed to improve the vascular supply and nutrition of the involved tissue, one of the important aspects of which is tissue oxygenation. To the extent that the latter is an important factor, it may also be achieved by the transvascular action of sodium succinate on tissue oxygenation. The combined use of vasodilators and the succinate is a possibility which we have not thoroughly explored as yet.

## CONCLUSIONS

Sodium succinate was administered intravenously to 10 patients with multiple sclerosis and orally over prolonged periods to 22 patients with multiple sclerosis. Subjective improvement was reported in 80 per cent and objective improvement was observed in approximately two-thirds of the patients by both methods of treatment. More prolonged follow-up observations on patients treated with the oral succinate have suggested that approximately one-half of them have been benefited. Beneficial effects consisted of (1) improvement in dyssynergia, ataxia, dysmetria, balance and gait; (2) improvement in the flexor withdrawal reflex and clonus in some patients; and (3) subjective improvement in the appreciation of vibration and objective improvement in position sense and skin writing.

Toxic effects were observed in one patient treated intravenously and in six patients given oral succinate. The latter toxic reactions consisted of gastro-intestinal and genito-urinary effects and were not alarming. Three of these patients were able to continue treatment with benefit on reduced doses. Deterioration of the patient's condition on discontinuance of the succinate was observed in four instances. They all improved on resumption of the treatment. Recurrent episodes have been observed in three patients.

The rationale for the use of sodium succinate in multiple sclerosis is discussed, and deductions with respect to its physiologic effects are considered in terms of the neuropathology of multiple sclerosis and other therapeutic approaches which have been tried in this condition.

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• The treatise embraces an introductory chapter, which relates to the instruments and apparatus employed in the diagnosis and treatment of diseases of the nervous system, and five sections. Of these, the first treats of diseases of the brain; the second, diseases of the spinal cord; the third, cerebro-spinal diseases; the fourth, diseases of nerve-cells; and the fifth, diseases of the peripheral nerves. Diseases of the sympathetic nerve are at present so little understood, if even one is recognized, that I have, for the present, deferred their consideration.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

# Diabetic Neuropathy and its Prognosis

*Samuel H. Epstein, M.D.*

ALTHOUGH the term diabetic neuropathy is of recent origin, the relationship between diabetes mellitus and lesions of the nervous system has received considerable attention for over a century. Nervous symptoms had been noted in the early literature cited by Desbonnets[1] and Marchal de Calvi,[2] but the latter is credited with the first description of diabetic neuritis in 1864. He pointed out that the neurologic lesions were the result rather than the cause of diabetes mellitus. His contribution was of particular significance at a time when current views, stimulated by the experimental work of Claude Bernard, held that diabetes mellitus might be caused by lesions of the nervous system.

Subsequent observations on neurologic manifestations in diabetes were summarized by Auché in 1890,[3] who described in detail the characteristic symptoms and signs, consisting of lancinating nocturnal pain, paresthesias, anesthesias, nerve tenderness, reflex changes, paralyses, and vasomotor and trophic disturbances. In the same year Charcot[4] reported typical cases of diabetes with paralysis and mentioned that the absence of knee jerks in diabetics was described by Bouchard in 1881. According to Woltman and Wilder,[5] Althaus in 1884 also reported neuritic signs of a pseudotabetic nature. Buzzard[6] likened the neuritis of diabetes to that of alcoholism and also pointed out the beneficial effects of reduction of glycosuria.

The literature from 1890 to 1935, as listed by Jordan,[7] emphasizes the widespread involvement of the nervous system among diabetics: pupillary abnormalities, neuritis of the optic nerve, extraocular palsies, acute abdominal symptoms, paresis of muscles of the bladder, psychic disturbances, etc. The incidence varies widely. Stewart[8] states that the nervous system is involved in 50 per cent of diabetic patients. Sevringhaus[9] re-

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ported pain in 49 per cent and reduced reflexes in 57.3 per cent. Jordan[7] noted decrease of one or more of the reflexes of the lower extremities in 45.3 per cent of 461 unselected cases of diabetes, but found actual neuritis in only 2.5 per cent of 1,000 consecutive cases. Rundles[10] found evidences of neuropathy in less than 5 per cent of 3,000 diabetic patients. Broch and Klövstad[11] noted polyneuritis in 20 per cent of 426 diabetics. In Rundles' monograph, the stipulation is made that the diagnosis of diabetic neuropathy should not be made unless neuritic symptoms are present and unless there are, in addition, definite signs of neurologic abnormality which persist beyond any period of acute diabetic nonregulation.

The clinical pictures of neurologic manifestations in diabetes were classified by Jordan[7] into three types: hyperglycemic, degenerative and neuritic. The first group included cases in which neuritic symptoms, not accompanied by signs of neuritis except tenderness, disappeared simultaneously with the reduction of glycosuria. The second group was comprised of those cases in which mild neuritic symptoms and signs began insidiously and tended to progress slowly over a period of years; those with circulatory deficiency in the legs were also included. The outstanding symptoms were pain, cramps and paresthesias of greatest intensity at night, and the signs included hyporeflexia and hypesthesia. The third type represented the cases of true diabetic neuritis and diabetic tabes, with relatively acute onset of severe neuritic symptoms or signs, usually followed by recovery. The overlapping between the last two types of neuropathy is obvious.

Another classification was suggested by Treusch.[12] The first group, called "diabetes with pain," is in every way similar to the hyperglycemic type of Jordan. The second group is called ischemic neuropathy and roughly corresponds to Jordan's degenerative type. In these cases there are definite evidences of obliterating arteriosclerosis and the neuritis has an insidious onset with pain, paresthesias and cramps, involving the legs primarily. The course is usually progressive, but occasionally considerable improvement occurs after many months if the vascular status of the extremity is improved. This was referred to by Root and Rogers[13] as neuritis with deficient blood supply. The third group includes cases of peripheral polyneuritis and polyradiculitis with secondary spinal cord changes. Onset in these cases is relatively acute with severe neuritic symptoms and definite neurologic signs, affecting the legs predominantly, but frequently involving other parts of the body. Improvement usually occurs in weeks or months. In about one-half of these cases the total protein content of the cerebrospinal fluid is elevated. This is the type of disorder

classed by Jordan[7] as true neuritis or tabes, neuritic type, and by Root and Rogers[13] as neuritis with paralysis. A fourth group is described as diabetic visceral neuritis and includes patients with burning paresthesias of the feet with objective vasomotor changes. This suggests primary autonomic nerve damage, which was emphasized by Rundles[10] who observed sweating deficiencies, loss of vasomotor and pilomotor control, dependent edema and certain types of skin alterations in patients with diabetic neuropathy. He described eight cases of orthostatic hypotension and orthostatic tachycardia in this group and points out a causal relation to autonomic nerve disease. In this paper only the so-called degenerative and neuritic types of neuropathy will be considered.

In a review of 100 cases of diabetic neuropathy by Rudy and Epstein,[14] no classification of cases was made, but diffuse involvement of the entire nervous system was emphasized. The great variety of neurologic signs and symptoms has been reported in the literature previously.[7, 10] Pupillary abnormalities have been noted occasionally and involvement of other cranial nerves has been observed, particularly in producing extraocular palsies.[15] The sixth cranial nerve appears to be most frequently involved, the oculomotor next and the trochlear last in order of frequency. The onset of these signs is usually sudden, without pain, and recovery under strict diabetic treatment is common.

Loss of urinary sphincter control is not infrequent. Jordan and Crabtree[16] reported seven cases of bladder paralysis, with neuritic symptoms in at least six of them. Gill[17] showed pathologic changes in the spinal cord in two cases of diabetic bladder. Rudy and Muellner[18] made cystometric examinations in 11 patients with diabetic bladder paralysis, 10 of whom showed neuritic signs. Rudy and Epstein[14] found neurogenic bladders without neuritic or pseudotabetic signs in 11 additional cases. Rundles[10] found genito-urinary and sphincter disturbances in 32 patients with diabetic neuropathy. As an accompaniment of diabetic neuropathy, he emphasized symptoms of gastro-intestinal dysfunction, sometimes referred to as "diabetic diarrhoea." He attributes this, along with the genito-urinary and sphincter disturbances in the same patients, to autonomic nervous system involvement.

The available pathologic data on neurologic complications of diabetes point to vascular disease as the underlying pathogenesis. The older literature is discussed by Woltman and Wilder,[5] who reviewed 42 cases, 20 of which showed degenerative changes in the spinal cord involving chiefly the posterior columns and the intramedullary portions of the posterior roots. They attributed these changes to arteriosclerosis. In 10 cases studied personally, they found marked thickening of the walls of the intraneural

vessels in the nerve trunks. They concluded that the factor of greatest significance is atherosclerosis. Griggs and Olsen[21] likewise emphasized the effect of vascular disease on the spinal cord in diabetes. Chemical analyses of diabetic nerves, reported by Jordan, Randall and Bloor,[22] showed that the phospholipid, cholesterol and cerebroside values were much lower than in normal controls, and these changes were correlated with the degree of arteriosclerosis present.

This review of the literature gives little indication of how neuropathy arises in diabetes, but arteriosclerosis appears to be a contributing factor from both the clinical and the pathologic standpoints. This applies to the true neuritic type of neuropathy as well as the so-called degenerative or ischemic type. In the present study of 50 cases of diabetic neuropathy, some consideration will be given to the clinical characteristics of these types, and an attempt will be made to evaluate the possible factors in the production of the neuropathy with particular reference to the role of vascular disease.

## REVIEW OF CASE MATERIAL

The sex incidence in this series was predominantly female, the ratio being 34: 16. The average age at onset of neuritis was 55.3 years, with the range from 27 to 80 years. Only three patients were under 40 years of age. Duration of diabetes before development of neuropathy was 6.1 years on the average, the longest being 22 years. In two cases diabetes was first discovered at the time of appearance of the neuritic symptoms. This does not imply that diabetic neuropathy actually preceded diabetes. In both instances other symptoms of diabetes were elicited at the time of examination and antedated the neuritic symptoms.

The type of onset was gradual or insidious in 42 cases. Only two patients experienced acute onset of severe neurologic symptoms, consisting of burning pains in the legs with ataxia and marked weakness. The remaining six cases in this series presented a subacute evolution of symptoms, developing over a period of several weeks.

Definite evidences of arteriosclerosis were present in 25 patients, all of whom were over 40 years of age. These included general as well as peripheral vascular disease. Evidences of local ischemia were found in 12 cases. None of the patients showed any degree of improvement in the neurologic condition and some became distinctly worse. In the group of cases without demonstrable vascular disease, in which there was no involvement of the peripheral vessels, the retina or cardiorenal system, definite improvement was noted in practically every one and complete recovery occurred in five of these cases.

No differences in neurologic manifestations were found in patients with or without arteriosclerosis. Muscular weakness in one or more extremities was observed in 23 cases of the whole series.

Pain was the cardinal symptom in 38 cases, and nocturnal exacerbations were noted in less than one-half of the cases. In 21 of these arteriosclerosis was not in evidence; the remaining 17 cases with pain were accompanied by arteriosclerosis. Pain was localized most commonly in the feet and legs, but in seven cases it was present in the hands alone. In one instance pain was localized in the back, and in another there was severe abdominal pain of segmental distribution; arteriosclerosis was present in both of these cases. Such symptoms are similar to those of tabes dorsalis.

Paresthesias alone were the major symptoms in 11 cases, and consisted of severe sensations of burning, pins and needles, tingling and numbness. Paresthesias were also present in all patients who had pain, regardless of the presence or absence of arteriosclerosis. Tenderness of the calves without objective sensory impairment was noted in 10 cases, and arteriosclerosis was present in only three of these.

Alteration of the deep muscle reflex was the most common neurologic sign. The Achilles reflexes were absent in 30 instances, the patellar in 35 instances. Complete absence of all deep muscle reflexes was noted in two cases and arm reflexes were diminished in 10 cases. These findings could not be correlated with the presence or absence of arteriosclerosis.

Superficial sensory impairment was observed in half of the cases. Deep sensibility was impaired more often. Vibration sense was diminished or absent in the ankles in 33 cases and was associated with impairment of position sense in 14 of these. In three cases position sense alone was lost. Involvement of deep sensibility occurs early in the disease, followed much later by impairment of superficial sensibilities. This was noted in the cases with arteriosclerosis as well as without.

The only other clinical manifestations encountered in this series of cases were atonic bladder present in two cases and Argyll Robertson pupils in one case. The latter patient showed evidences of polyneuritis involving all four extremities. The patients with urinary sphincter disorder showed a pseudotabetic picture. Arteriosclerosis was present in one of these.

Cerebrospinal fluid was examined in 22 cases; of these, 15 (nearly 70 per cent) showed an elevation of the total protein content between 50 and 140 mg. per hundred ml. There were no other abnormal findings. A direct correlation was observed between severity of the neurologic disturbance and the higher total protein values. Though 10 cases in the

arteriosclerotic group showed elevated total protein, the highest values were obtained in cases without arteriosclerosis.

Only eight patients developed neuropathy when diabetes was well controlled. Definitely poor regulation was present in 29 cases, and in nine of these there was manifest acidosis at the onset of neuropathy. In four cases, previously well regulated, infection preceded the development of neuropathy and probably disturbed the control of the diabetes at least temporarily.

In only five cases was there evidence of poor dietary intake with possible vitamin deficiency. An alcoholic factor was evident in four other cases, and in these the clinical picture was indistinguishable from that of alcoholic neuritis. The role of diabetes in these cases could not be determined.

## DISCUSSION

This series of cases of diabetic neuropathy presents some points of clinical difference from previous reports. The age of onset in the present series is greater than in Rundles' series,[10] in which one quarter of the patients were less than 40 years of age. Moreover, he found no significant degree of occlusive vascular disease in 80 per cent of 125 cases. One-half of the present patients showed definite evidences of arteriosclerosis, and in half of these local ischaemia of a limb was present. This appeared to mitigate against recovery of neurologic symptoms. Since improvement was manifest only in the group of patients without demonstrable vascular disease, it must be concluded that arteriosclerosis is a factor of prognostic significance. From the practical standpoint, the most useful classification of diabetic neuropathy would be based upon the presence or absence of associated vascular disease. The latter fits best into the category of true neuritis and the former may be considered degenerative or ischemic.

The neurologic manifestations of these two types could not be distinguished from each other. Analysis of the signs and symptoms in this series of cases showed essentially no differences in motor signs, individual nerve involvement, pain, paresthesias, deep muscle reflex changes and objective sensory impairment. In the clinical study by Kauvar[23] it was likewise noted that manifestations of peripheral neuritis were similar in all respects to those produced by ischemia of the extremities. These similarities were also apparent in the work of Wortis, Stein and Jolliffe[24] on the effect of asphyxia upon the function of the peripheral nerve. Apart from some tendency towards asymmetrical involvement, the clinical features

of the peripheral neuritis observed in these cases are not clearly distinguishable from chronic neuritides of other origins.

The type of sensory impairment in these cases is worthy of note. The characteristic order of sensory changes, loss of deep sensibility followed by loss of superficial pain sensibility, is similar to that observed by Wortis et al. in experimentally induced ischemia of a limb and in clinical occlusion of blood supply to an extremity. This was attributed by them to the resistance of the smaller, non-medullated (C) fibers, in contrast to the more vulnerable, faster conducting, medullated (A and B) fibers in the peripheral nerve. This work suggests that those portions of the peripheral nerve which conduct impulses at higher rates of speed and which are more irritable have the highest metabolic requirements and are most susceptible to metabolic disturbances.

The elevation of total protein content of the cerebrospinal fluid in a very large percentage of the cases reported here merits some comment. The occurrence of the highest total protein values in the cases unassociated with arteriosclerosis is noteworthy. Joslin and Root[25] stated that the magnitude of the total protein increase parallels the severity of the neuropathy. Rundles[10] found values of 268, 364 and 426 mg. per hundred ml. in patients with more severe forms of the disease. This increase is not pathognomonic of diabetic neuropathy, since it occurs characteristically in acute infective polyneuritis. However, it indicates that involvement of the nervous system in diabetes extends at least into the posterior nerve roots. The posterior columns may become affected secondarily, but pathologic evidence of primary spinal cord involvement is not conclusive.

Impairment of bladder function in two cases was associated with signs of posterior root involvement similar to those seen in tabes dorsalis and in combined system disease. However, it has been suggested that sphincter disturbances are due to disease of the sacral and pudendal nerves,[10] and this may be the case in diabetic patients with urinary disorders and impotence. Such involvement may also account for cases of diabetic neurogenic bladder without neuritic or pseudotabetic signs. There is, nevertheless, no conclusive evidence whether bladder paralysis in diabetic neuropathy is due to primary sensory loss or to motor impairment as well. Early loss of deep sensibility suggests that it is a sensory disorder. In this series of cases there was insufficient evidence to evaluate the role of vascular disease in bladder disorders, and no such correlation exists in the literature.

In considering the precipitating factors in production of diabetic neuropathy, neither acidosis nor glycosuria are said to be of importance. Yet it is noteworthy that in 18 per cent of the present cases onset occurred

in the presence of acidosis. The majority of cases of diabetic neuropathy were associated with prolonged poor diabetic control. This corresponds with the observations of Joslin[26] et al. who state that symptoms of neuropathy always start during a long period of uncontrolled diabetes. Almost 20 years ago, Root and Rogers[13] concluded that the diabetes itself exerts some specific toxic effect upon the spinal cord or peripheral nerves, which is dependent primarily upon abnormal nutrition of the inadequately controlled stages of the disease.

The role of vitamin deficiency was discussed by Root[27] as early as 1922. Wohl[28] found clinical evidences of avitaminosis in a diabetic, and investigated the nutritional state in diabetic neuritis, concluding that vitamin deficiency was the cause of neuropathy. Cobb and Coggeshall[29] included diabetic neuritis among other nutritional neuritides, such as that of alcoholism and beri-beri. Needles[30] found the vitamin $B_1$ content of the diet adequate in two cases studied, and considered the role of defective absorption or utilization of the ingested vitamin. He later[31] discarded this idea when he found no improvement in seven cases treated with thiamin chloride and noted normal thiamin excretion values measured according to the tolerance tests utilized by Pollack, Ellenberg and Dolger.[32] The therapeutic benefit reported in nine ambulatory cases by Fein, Ralli and Jolliffe[33] must be evaluated in the light of the mildness of the neuritis. In a recent study, Broch and Klövstad[11] found no support for the assumption that the polyneuritis in diabetes is due to vitamin $B_1$ deficiency but found a good deal of evidence in favor of a circulatory disorder. The critical review of Meikeljohn[34] throws considerable doubt as to whether thiamin is the antineuritic vitamin. Personal experience suggests that the clinical results of vitamin treatment in diabetic neuropathy are not convincing.

## CONCLUSIONS

Diabetic neuropathy is best classified from the prognostic point of view into two types: (1) cases associated with arteriosclerosis, and (2) cases without demonstrable evidence of vascular disease. The latter type indicates a good prognosis, whereas the prognosis is distinctly poor in the former. There is little if any improvement in cases in which arteriosclerosis is present, and usually there is progression of the symptomatology. The patients without arteriosclerosis are usually under 40 years of age, in contrast to the older age of cases associated with arteriosclerosis. Poor control of diabetes in either type plays a role in the precipitation or aggravation of neuropathy.

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# Aphasia in a Deaf Mute

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GESTURAL systems of language as a method of communication are considered to have preceded oral speech by eons. There are said be seven hundred thousand distinct elementary gestures, produced by facial, manual or digital movements or by body postures and various combinations of such motions. These would be sufficient to provide the equivalent of a modern language in its entirety.[1] Some of these gestures are universal in character and are found in civilizations widely separated in space and time; systems of dactylology provide substitutes for the spoken word in specific languages. Lip reading is still another form of gesture for the spoken word; it becomes a phase of spoken language when it results in audible speech for deaf mutes.

This paper describes a case wherein an organic cerebral lesion resulted in disturbances in the gesture language function, which had served as the patient's primary method of communication.

The occurrence of aphasic disturbances in deaf mutes following cerebral lesions was postulated by Hughlings Jackson in 1878.[2] Later Kussmaul[3] wrote that aphasia applied not only to speech disturbances, but to disorder of any of the functions of communication. Dejerine[4] in 1914 further defined aphasia as the loss of the memory of signs by which men exchange ideas with each other. In view of the general acceptance of these concepts it becomes a matter of considerable surprise that there are so few references in the literature to actual cases of aphasia in deaf mutes. Critchley[5] reported the first case in English in 1938, and cites a case from a French publication of 1896 by Grosset.[6] The following case represents the third in which aphasic disturbances were studied in a deaf mute. It differs in some important details from the previous two.

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REPORT OF CASE

A 43 year old congenital deaf mute first noticed dizzy spells, apparently not severe enough to bring him to medical attention, in January 1947. Otherwise he was in good health. On May 21, 1947, during a severe episode of vertigo, he fell to the ground, struck the left side of his head and was unconscious for about 30 minutes. He suffered some abrasions and contusions about the face and injury to the left shoulder. Otherwise the physical and neurologic examinations were negative. X-ray of the skull revealed a linear fracture of the left parietal bone. On June 2, 1947 he suffered a clonic convulsion without loss of consciousness, which lasted four hours and involved only the right upper extremity. Neurologic examination at the time disclosed only transient weakness of the right arm and hand; spinal fluid was within normal limits. The electroencephalogram disclosed a variable basic frequency in the occipital leads, and an amplitude asymmetry between the right and left posterior leads, not consistently maintained but present for a significant percentage of the record. All posterior leads showed a higher pattern on the left than on the right.

During the next three weeks there was a slight fluctuating weakness of the right arm which increased gradually. There was associated cramping in the right hand, lasting a minute or more and recurring every few hours. The right grip became progressively weaker until the thumb could no longer be abducted. On June 23, 1947, after a period of intense Jacksonian twitching of the right cheek and the right upper extremity, flaccid paralysis of the right upper extremity supervened, though abduction was retained in the right shoulder. There was no loss of consciousness during these convulsions. Biceps, triceps and supinator reflexes were depressed. There were no sensory alterations. Other neurologic signs were normal. During the course of examination the patient developed a Jacksonian convulsive seizure which started in the right trapezius and spread to the right side of the face and finally to the right arm. The entire episode lasted five minutes, and was unaccompanied by any disturbances of consciousness. Following this seizure he complained of a burning pain in the arm. Spinal fluid was normal except that the initial pressure was 195 mm. of water and the Ayala index was 6.4.

All communications with the patient were effected through an interpreter who was conversant with finger spelling, or through the medium of writing questions and answers. The patient's father assisted in furnishing the history and in making some of the examinations. The patient was intelligent, had achieved the equivalent of a high school education and been "good at figures," and had become president of his lodge. While in the hospital, he was able to use the left hand for conversing and writing during periods of weakness or paralysis of the right arm and hand. No previous disability in use of dactylology or in understanding it had been noted during these periods of motor disturbances of the right upper extremity.

On June 24, 1947 a pneumoencephalogram demonstrated normal ventricular and subarachnoid patterns. One day later the right lower extremity became paralyzed, and at the same time the patient became mentally clouded. He could not communicate with people about him. His father called our attention to this, stating that the patient had "lost his mind." He did not recognize anyone in the family and could make no contact with them. Some hours later paralysis extended to involve the entire right side, including the face. The extremities were useless and flaccid. Deep tendon reflexes on the right were increased. Right Babinski and Hoffmann signs were present. Plantar reflexes on the left were equivocal. Cutaneous sensation was intact. When the mental

confusion cleared it was evident that the patient could not use his left hand either for finger spelling or for writing, though there were no other signs of apraxia in the left hand. He had lost the minimal ability previously present to utter some words. He could not utilize "universal symbols," the so-called shorthand of deaf mutes. He could neither spell with the left hand, nor could he understand finger spelling. He did not recognize his children's names, nor could he spell them out. He could not read the sign language. In two days he began to recognize people about him, particularly members of his family, whose names he could now speak. It was a week before his father declared that "his mind was good again." By this time he could again make use of universal hand movements. On June 27 it was noted that the patient could read script and print, but still could not read the sign language. In fact he preferred to ignore finger conversation, whereas he enjoyed reading the newspaper.

On July 2, 1947, his speech function was appraised as follows: He could follow any tongue imitations necessary for the production of speech. There was no paralysis of the tongue. His reading had not been affected. From cursive script he was able to pick out objects to perform simple commands, such as hold up two fingers, "give me the paper," etc. He was able to lip read some commands. There was a reduced ability for finger speech. He could spell the alphabet up to J and no further. While he could understand some questions such as "How many children have you?" from written questions, he could not understand and respond to the same question from finger spelling. The patient seemed despondent, but his spirits were revived when it was shown that he was able to give some response. The patient could not respond to written questions with finger spelling, nor could he make his thoughts or wants known, either in finger spelling or in writing. He could not answer a question given in finger spelling with a finger spelling answer. He was able to finger spell correctly the names of a number of objects after a short while of encouragement and teaching. He was, however, unable to give back finger spelling language in answer to questions.

A craniotomy was performed on July 15, 1947. Before the operation his speech disturbance had improved progressively although slightly; up to the time of the operation the patient still had a good deal of difficulty in communication with anyone else. Three days prior to operation he could identify a pen, tray and money, but he would not or could not indicate their use. He could not spell out the words. During this examination it was demonstrated he recognized laterality. There was no apraxia of the left hand.

A left fronto-parietal craniotomy was performed which exposed a very tense dura. A small opening in the dura near the parasagittal line and in the region of the coronal suture was made to pass a ventricular needle, which was directed toward the lateral ventricle. As this was done 20 ml. of chocolate colored, old bloody fluid escaped under pressure, indicating the presence of a cystic cavity or an intracerebral clot which was displacing the ventricle. The dura was then completely opened, exposing the frontal convolutions and the Rolandic vein. The second frontal convolution appeared yellow and ischemic in its inferior and posterior portions. An area of cortex comprising the posterior portion of the second frontal convolution, approximately 3 cm. in diameter and about 2 cm. in depth was coagulated and excised in one plug. This unroofed tumor tissue in the subcortex which extended in a vertical direction for a distance of 5 cm. and medially for 5 cm. The tissue was purple-red in color, containing numerous blood vessels and having the appearance of a tumor which had undergone a recent hemorrhage. The tumor, entirely subcortical in its extent, involved the posterior halves

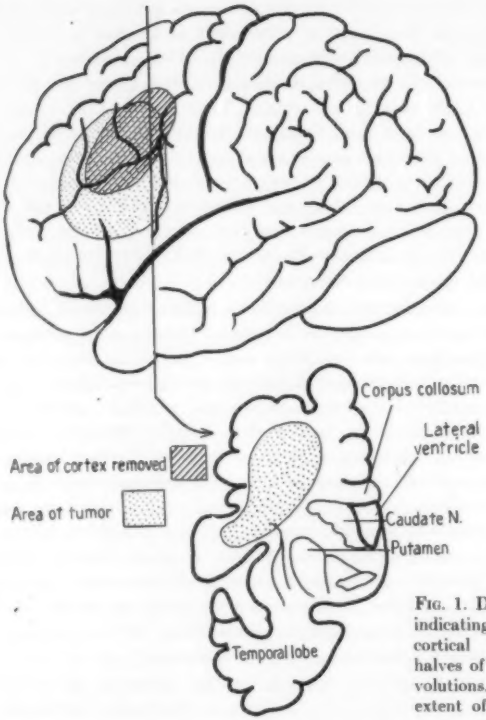


FIG. 1. Drawing of left cerebral hemisphere indicating location and extent of the subcortical tumor, involving the posterior halves of the second and third frontal convolutions. The shaded area indicates the extent of cortical excision at operation.

of both the second and third frontal convolutions. Apparently the anterior tip of the internal capsule was invaded by the neoplasm, but it seemed that the external capsule was spared. The cortex of the entire third frontal convolution was intact, whereas the posterior portion of the second frontal convolution was excised during the operative procedure (figure 1). Complete excision was impossible. Microscopic examination showed the tumor to be a spongioblastoma (glioblastoma) multiforme.

Following the operation hemiplegia on the right side became complete and spastic. Eight days postoperatively it was noted that the patient could again communicate, utter a few words, and converse with "shorthand" gestures. On further examination July 28, nine days postoperatively, the patient had no difficulty with ordinary dactylologic conversation for the first time since onset of the aphasia. He could name some common objects. However, there was some difficulty in spelling. There was no apraxia nor had any been found at any time during the course of the speech disturbance. There was no defect in reading. He could spell out the names of common objects shown to him; he could also read finger spelling. Over the next several days speech improvement was rapid, so that when he left the hospital he could finger speak spontaneously, but not as fluently as he had before the onset of the aphasia. He seemed to have occasional difficulty in remembering how to spell.

The patient was discharged from the hospital on July 31, 1947. At the time of the discharge from the hospital there was a residual right hemiplegia, with minimal involvement of the face. At home he made progress, and, with recovery of the use of the right leg, he could walk about. The right upper extremity remained spastic and paralyzed. By September 15 he had regained the maximum speech function, but there appeared to be some lessening of his intellectual faculties and he was euphoric. With the recurrence of convulsions on September 24, 1949, his condition deteriorated. Jacksonian attacks involved the right lower extremity; paralysis recurred; finger spelling again became impaired so that his capacity became about one-fourth of what it had been. In November he became completely hemiplegic and eventually became stuporous. He died at home on December 1, 1947. No autopsy was obtained.

## DISCUSSION

This paper is concerned primarily with the aphasia which apparently developed only after hemorrhage into a left frontal lobe tumor. It is presumed that the spinal air injection precipitated the hemorrhage. The appearance of the bloody contents of the tumor was consistent with a period of three weeks, the interval elapsing between pneumoencephalography and craniotomy. Hemiplegia, mental disturbances and subsequent loss of communication functions followed immediately after the air injection. Judging from the history the tumor may be presumed to have been present at least six months before focal symptoms of Jacksonian convulsions and motor weakness became apparent.

The tumor, entirely subcortical, was located in the posterior halves of the second and third left frontal convolutions. It did not affect the cortex of the inferior convolution, but at operation was observed to be exerting pressure on the second. Decompression by evacuation of the bloody contents of the tumor resulted in prompt amelioration of symptoms, both with respect to the speech disturbance and the motor weakness of the lower extremity.

Of the two cases of aphasia in deaf mutes previously reported, Critchley's was a 42 year old man who lost his hearing at seven years of age. He had first learned finger spelling and at a later date, lip reading. Following a cerebrovascular lesion with hemiplegia he lost the articulative speech he had acquired and exhibited agraphia. He also lost the ability to write simple calculations, to communicate with his hands, to understand finger spelling and to lip read. There was partial return of some of these functions, but he persisted in a dysarthric, ungrammatical speech which he could not modulate. His finger speech remained the most severely impaired of all of his speech functions.

Grosset's patient was a 50 year old arteriosclerotic with cerebrovascular disease. Normally he conversed only with his right hand. After

onset of symptoms he could no longer spell with the right hand, but could do so promptly with the left hand. There was agraphia in the right hand, but no alexia or agnosia for finger spelling. This patient had learned finger spelling normally only with the right hand. Critchley's patient spoke with both. Ours was reported to have conversed primarily with the right hand, but he had to use the left hand when the right was incapacitated.

Critchley regarded his case as one of dactylologic apraxia, and Grosset's one of apraxia, possibly one of finger agnosia. He attempted to explain the retention of finger speech in the left hand of Grosset's patient by emphasizing that French deaf mutes use only one hand, like Americans, and unlike British, who use both hands. He believed that Grosset's patient retained the integrity of his preverbal processes and intact internal speech. This was not true in Critchley's patient. Grosset had postulated tentatively a center for manual speech in deaf mutes in the cortex of the left second frontal convolution.

The conceptions of agnosia, apraxia and aphasia by Nielsen,[7] in his formulation of the disturbances of the function of language, have been useful for our understanding of the loss of these functions in our patient. The language disorder was comprised of apraxia and agnosia of the finger movements in dactylology, and agraphia of the left hand. (The right hand was paralyzed.) The patient retained the ability to read and understand the written and printed word. He retained all praxic and gnostic functions of the hand, except when the hand was used for communication. With the recovery of some of the dactylologic functions, a small measure of lip reading was observed, though this faculty was very limited even in his healthy state. Although the apraxia and agnosia for finger spelling receded rapidly after the tumor decompression, agraphia persisted for the remaining months of the patient's life. A writing center had been postulated by Exner[8] at the foot of the major second frontal convolution. This area had been flattened and ischemic preoperatively and was excised at operation.

The symptoms apparently arose from the tumor in the left frontal lobe. It is presumed that there were no remote vascular or pressure effects. Thus, only the association fibers from Broca's convolution and from the second convolution together with the writing center itself were destroyed. These lesions alone must account for the language defects. Broca's convolutions, according to Nielsen, contains the patterns of motor speech. Thus, whether the motor speech is articulative, or merely digital-gestural in character, a lesion such as was present in our patient would render him speechless.

The apraxia for finger speech appears to be unrelated to the lesion in

the second frontal convolution, since there was considerable recovery of this function even though the posterior part of this convolution had been excised. It might be argued that this recovery was due to functioning of the minor side; some doubt is cast upon this argument by the rapid recovery after evacuation of the blood clot from the tumor, and the recurrence of the disability with regrowth of the tumor. The persistence of agraphia indicates that the minor writing center was not functioning. It would seem that the apraxia for finger speech is as much related to lesions affecting Broca's convolution and its association pathways as is the apraxia for articulative speech.

Nielsen's concepts further provide an explanation of dactylologic agnosia. He states that the angular gyrus contains in its cortex patterns for revisualization of the written and printed word. In our patient these patterns were undisturbed. However, patterns for revisualization of finger spelling were affected, producing a special form of reading disability. The dissociation between the ordinary and dactylologic form of reading, under the pathologic conditions present in this case, would depend on the difference in the process of learning each form of reading. The deaf mute learns to read script and print silently. He does not hear or attempt to articulate the words he reads. It is Nielsen's belief that under such circumstances the angular gyrus is independent of the frontal speech centers, and a lesion in the frontal lobe does not produce visual verbal agnosia (alexia). In the dactylologic function, however, there is a close and continued association between spelling the words with the fingers, and reading the words as they are spelled. This interdependence of the praxia and gnosia results in a strong dependence of the angular gyrus upon Broca's convolution for gnostic functions. It is not unlike those cases in children who have not yet learned to read without moving their lips. In such cases inability to recognize the written or printed word results from a lesion in Broca's convolution, in spite of an intact angular gyrus.

This case, therefore, suggests a situation in which, though the engrams for the written and printed word in the angular gyrus were independent of Broca's convolution, the engrams for finger spelling were decidedly dependent on the frontal centers. The lesion in the subcortex of the left third frontal convolution rendered the patient incapable of understanding finger speech, while he retained his ability to read.

Universal hand gestures are more primitive than finger spelling and, as a short hand method of expressing words and ideas by a single movement, are more heavily weighted by affective qualities. No previous case had recorded the loss of this function in deaf mutes, although the possibility has long been anticipated. An intimate association between this

function and that of verbal speech in this patient becomes apparent. The only words which the patient could utter were names of members of his family or other words of similar affective association. The two functions, loss of hand gestures and vocal speech, disappeared simultaneously at the onset of the aphasia and returned virtually simultaneously within a few days, long before dactylologic function became adequate. These observations are consistent with the many that record affective speech as the earliest to recover in an aphasic disorder.

## CONCLUSIONS

1. A congenital deaf mute developed apraxia and agnosia for dactylology and agraphia in the unparalyzed left hand, following a hemorrhage into an infiltrating glioma involving the posterior portions of the left second and third frontal convolutions.

2. Apparently the dactylologic disturbance resulted from the lesion in the subcortex of the third frontal convolution and the agraphia resulted from the lesion in the posterior portion of the second convolution.

3. An explanation is offered for the dissociation between the dactylologic and verbal gnosia.

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By aphasia is understood a condition produced by an affection of the brain by which the idea of language, or of its expression, is impaired. The word is derived from the Greek—α, privative, and φασις, speech—and, as stated by Trousseau, was proposed by M. Chrysaphis, a distinguished Greek scholar, as a substitute for *alalia*, used by Lordat, and *aphemia*, employed by Broca, to designate the same condition.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

# Medical Treatment of Psychomotor Epilepsy

*Jerome K. Merlis, M.D.*

THE MODERN APPROACH to the non-surgical treatment of epilepsy emphasizes mental hygiene and the use of a few selected drugs. Psychotherapy is practiced formally and informally, consciously and unconsciously, and usually as an adjunct to drug therapy. Its results are difficult to assess, and drug therapy continues to be the mainstay of treatment.

The methodology of the use of anti-epileptic drugs is empiric. Laboratory investigation may yield data demonstrating that a given drug has a protective action against induced convulsions, but as yet there is no method which will indicate the value of a drug in psychomotor epilepsy nor, indeed, in any form of epilepsy, short of adequate clinical trial.

Adequate clinical evaluation of a new drug is a troublesome task. In the case of the anti-epileptic drug, the difficulties are compounded by the peculiarities of the paroxysmal disorders of consciousness known as epilepsy. All who work with epileptics are well aware of the unassessable imponderables which influence the frequency of seizures and which make it dangerous to generalize from observations of marked improvement in occasional cases.

In essence, the evaluation of a new drug is a statistical problem. Studies must be carefully planned, for certain requisites in terms of case selection, controls, duration of observation, etc., are essential before a study may profitably be analyzed statistically. Fisher[1] has stated that, "in a real sense, statistics is the study of populations or aggregates of individuals, rather than of individuals." In the usual study of an anti-epileptic drug the total group of patients is small and the breakdown into

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Read at a combined meeting of the American Academy of Neurology and the American Chapter of the International League Against Epilepsy, Cincinnati, Ohio, April 15, 1950.

TABLE 1

| *Drug* | *Authors* | *No. of Cases* | *Controlled* | *Greatly Improved* | *Moderately Improved* | *Slightly Improved* | *Unchanged or Worse* | *% Improved* |
|---|---|---|---|---|---|---|---|---|
| DILANTIN | Merritt & Putnam (2) | Psych. alone 19<br>Psych. & GM 20 | 12<br>12 | 5<br>4 | 2<br>4 | | | 100<br>100 |
| | Williams (3) | Psych. alone 4<br>Psych. & GM 7 | 1 | | 6 | | 4 | 64 |
| | Lauriat & Lauriat (4) | Psych. & GM 2 | | | 2 | | | 100 |
| | Weinberg-Goldstein (5) | Psych. & GM 1 | | | | | 1 | 0 |
| | Gardner (6) | ? | 71% | 29% | | | | 100 |
| TOTAL NO. OF CASES—53 | | | TOTAL IMPROVED—48 | | 91% IMPROVED | | | |
| TRIDIONE | DeJong (7) | Psych. 3<br>Psych. & GM 22<br>Psych. & GM 3 | 7 | 17 | | | 4 | 86 |
| | Davis & Lennox (8) | 41 | 7 | 7 | 12 | | 15 | 63 |
| | Davidoff (9) | 12 | 6 | | | | 6 | 50 |
| | Perlstein (10) | 6 | | 5 | | 1 | | 100 |
| | Simons (11) | 3 | | | | 1 | 2 | 33 |
| | Davies & Spillane (12) | 5 | | | | | 5 | 0 |
| | Verjaal (13) | 6 | 1 | 2 | | | 3 | 50 |
| TOTAL NO. OF CASES—101 | | | TOTAL IMPROVED—66 | | 65% IMPROVED | | | |
| MESANTOIN | Kozol (14) | Psych. 10<br>Psych. & GM 17 | | 9<br>12 | 1 | | 1<br>4 | 90<br>76 |
| | Loscalzo (15) | Psych. & GM 12 | Reduction insufficient to be of statistical value | | | | | ? |
| | Aird (16) | 14 | 7 | | 4 | | 3 | 79 |
| | Lennox (17) | Psych. 2<br>Psych. & GM 3 | | | ? 2 | | 3 | ca 40 |
| | Arieff (18) | Psych. & GM 5 | | | | | 5 | 0 |
| TOTAL NO. OF CASES—63 | | | TOTAL IMPROVED—35 | | 56% IMPROVED | | | |
| PHENURONE | Gibbs et al. (19) | 58 | | 29 | | | 29 | 50 |
| | Carter et al. (20) | 12 | | | 2 | | 10 | 17 |
| | Davidson & Lennox (21) | Psych. 23<br>Psych. & GM 37 | | | 10<br>11 | | 13<br>26 | 43<br>30 |
| | Livingston & Kajdi (22) | Psych. (idio.) 38<br>Psych. (org.) 8 | 20<br>2 | 6<br>1 | 4 | | 8<br>5 | 79<br>38 72 |
| | Little (23) | ? | | | 66% | | | 66 |
| | Abbott Co. Compilation | 128 | | 57 | 28 | | 43 | 66 |
| TOTAL NO. OF CASES—176 (Excluding Abbott Co. Compilation) | | | TOTAL IMPROVED—85 | | 49% IMPROVED | | | |

smaller and smaller subgroups according to etiology, type of seizures, age of onset, etc., makes the study essentially one of individuals rather than of statistically significant aggregates. The problems of clinical classification and grouping, the necessity for long term observation and the natural desire to afford whatever help is possible to these unfortunate patients are great barriers to scientific planning and accomplishment. Adequate control measures are difficult to achieve, and such accepted methods as the use of matched treated and untreated groups and the administration of placebos are conspicuous by their absence.

It is not surprising, therefore, that the literature abounds in expressions of opinion and is sorely lacking in quantitative data. Table 1 presents the total of such data found in an intensive search.[2-22, 40] No information on phenobarbital could be tabulated because the category, psychomotor epilepsy, has only relatively recently come into general use in the classification of the epilepsies.

It is to be noted that the number of patients in each group is small, and that the total number of patients reported for all the drug studies is less than 400. Such small samples make the presentation of percentages expressions of simple arithmetic rather than of statistics. Individual studies have their own inherent shortcomings and are not comparable since the methods of case selection, diagnostic classification, dosages used, combinations with other drugs, duration of treatment, etc., vary significantly.

If a number of workers using a drug under diverse conditions of study arrive at the same conclusion, it may be reasonable to infer that many of the defects of the original studies have cancelled out and that the conclusion contains at least a measure of truth. If these data, therefore, are accepted at their face value, Dilantin, Tridione, Mesantoin, and Phenurone must be considered as having definite value in the treatment of psychomotor epilepsy.

## CHOICE OF DRUG

Therapeutic effectiveness must be balanced against toxicity. The new drugs have brought into sharp focus the problems of drug toxicities such as exfoliative dermatitis, nephrosis, liver damage and blood disorders. In terms of mortality, the blood dyscrasias represent the most serious toxic complication. Data are available on 30 cases of serious blood disorder attributed to anticonvulsant drugs, 15 of which have been fatal (Table 2).[23-47] Whether or not phenobarbital ever produces such dyscrasias is a matter of dispute, but it is clear that all the other modern anticonvulsants in common use have been implicated in greater or lesser degree. Aside

from one case of a leukemic disorder,[48] all the dyscrasias have been classified as aplastic anemia or agranulocytosis.

There is a general tendency to feel that so long as blood counts are made periodically, the danger of occurrence of serious blood dyscrasia is minimized. It is well to examine briefly some of the available evidence pertaining to blood disorders due to drugs. The data on the anti-epileptic drugs themselves are not sufficient for analysis of the pathogenesis of these disturbances, and recourse must be made to knowledge obtained through careful study of other drugs such as amidopyrine, the sulfonamides and the thiouracils. It appears probable that all drugs which produce blood dyscrasia act in a fundamentally similar fashion.

TABLE 2

BLOOD DYSCRASIAS ATTRIBUTED TO ANTI-EPILEPTIC DRUGS

| *Probable Toxic Agent* | | *No. of Cases* | *Duration of Treatment Before Onset* | *Recoveries* | *Fatalities* |
|---|---|---|---|---|---|
| Dilantin | 23-25 | 3 | 1-2 months | 3 | 0 |
| Tridione | 26-36 | 13 | 1 week to 13 months | 6 | 7 |
| Diphenylene and/or Tridione | 37 | 1 | Diphenylene 11-12 mos.<br>Tridione 3-4 mos. | 0 | 1 |
| Tridione and/or Mesatoin | 38 | 1 | Tridione 5 mos.<br>Mesantoin 4 mos. | 0 | 1 |
| Mesantoin and/or Thyphentoin | 39 | 1 | Mesantoin 12 mos.<br>Thyphentoin 2 mos. | 1 | 0 |
| Mesantoin | 40-46 | 8 | 6 days to 9 months | 4 | 4 |
| Phenurone | 45-47 | 2 | 2 months | 0 | 2 |

The marrow disturbance due to such drugs may be total or selective. The process may be one of toxic depression of one or more of the bone marrow elements, or there may be an allergic manifestation with the bone marrow acting as the shock organ.[49]

A mild depressant action on the bone marrow is a common finding with many drugs. That the anti-epileptic drugs exert such an action is indicated by Davidoff's report[9] that in 46 of 75 patients under treatment with Tridione, there were changes in the blood count, in most cases involving the white blood cells. Davis and Lennox[8] have reported that 20 per cent of 127 patients on Tridione had a neutrophile count of 3,000 or less, 13 per cent being under 2,500. Eight of Whitty's[50] 26 cases on Tridione for six months or longer showed a decrease in granulocytes. In the case of Mesantoin, Loscalzo[15] has reported that in 67 patients, 40 per cent showed a moderate increase of lymphocytes at the expense of polymorphonuclear cells. Fetterman and Victoroff[51] report an eosinophilia and relative monocytosis in 20 of 100 patients on Mesantoin. On the basis of such data it

appears reasonable to consider that these drugs are bone marrow toxins which, in the dosage range usually used, affect the blood-forming tissues in 20 per cent or more of the patients receiving the medication.

Two possible situations exist: (1) a drug which is a bone marrow toxin may eventually produce a severe depression of the blood-forming tissues giving the picture of a pancytopenia; or (2) agranulocytosis or pancytopenia may occur in an explosive fashion on an allergic basis in an individual with a normal or a depressed marrow.

PROGNOSTIC VALUE OF PERIODIC BLOOD COUNTS

The common practice of discontinuing medication when a definite leukopenia appears is an obstacle to the determination of whether or not the gradually developing neutropenia, so frequently noted during medication, ever becomes the more serious agranulocytosis or pancytopenia. Indeed, the only evidence available indicates that this toxic manifestation is, in a sense, self limiting, for the blood count tends to return to normal during continuous administration of the offending drug. Thus, Young[52] reports a case under treatment with thiouracil in whom, after fourteen days of treatment, the count had fallen from an initial 3,000 neutrophiles in a total of 5,600 white blood cells to 1,480 in a total count of 3,900. At this point the dose of thiouracil was doubled. Four days later the counts were essentially the same, and after another six days the count had increased to 6,100 with 3,500 neutrophiles, despite continuous administration of the drug. In the Davis and Lennox[8] study, two of the patients whose neutrophiles had fallen to less than 1,600 were continued on Tridione. During the continuous administration, subsequent neutrophile counts were above 2,700. It is questionable whether or not discontinuing the responsible drug influences the course of the blood disturbance. Nixon, Eckert, and Holmes[53] have reported recovery in three patients with sulfa drug agranulocytosis despite the fact that the responsible drug was continued because of overwhelming infection.

It is to be noted that the changes in the bone marrow may be well established before they are reflected in the peripheral blood. Cessation of medication even before the appearance of signs in the peripheral blood may not prevent the development of the agranulocytosis.[55]

Early diagnosis of the dyscrasia through periodic blood counts does not appear to influence mortality rate. In an analysis of the data on 74 cases of sulfa drug agranulocytosis, Young[52] found that the rate was essentially the same in patients who had received no blood study as in those who had received periodic blood counts. In one case, five counts were made in the six days preceding agranulocytosis, and, although treat-

ment was stopped when the count fell from 12,500 to 8,500, the patient died.[55] In another case, agranulocytosis developed even though sulfa was discontinued at a white blood count of 7,800 with 5,694 neutrophiles.[56]

If, however, it is felt that blood counts should be done, it is important to decide at what point in a declining blood count the offending drug is to be discontinued. An empirical limit of 1,600 neutrophiles has been recommended by Davis and Lennox.[8] In one of the cases reported by Briggs and Emery,[27] Tridione was discontinued when the neutrophile count fell below 2,000, but it continued to fall to a low of 100. In another case cited by Forster, Watson and Neumark,[29] Tridione was discontinued at a neutrophile count of 2,400 and was resumed when the count rose to 4,500. It was again discontinued when the count had fallen to 2,100, but this time the fall continued with death resulting.

There is little to indicate, therefore, that periodic blood counts do much more than provide the physician with a false sense of security. In terms of the morbidity of blood dyscrasia and other serious toxic phenomena, the safest of the anti-epileptic drugs are phenobarbital and Dilantin. Available data indicate that Dilantin, alone or in combination with phenobarbital, is effective in a certain percentage of patients with psychomotor epilepsy. The most rational approach to drug therapy would appear to be the exploitation of these drugs to the limits of their usefulness before using others considerably more dangerous. Mesantoin, Tridione and Phenurone should be used only as calculated risks after careful consideration of each case on its individual merits.

SUMMARY

1. Quantitative data on the drug treatment of psychomotor epilepsy are rare. The case-series are small in number and are of questionable statistical validity. However, on the basis of available data, Dilantin, Tridione, Mesantoin and Phenurone may be considered to be of some value in therapy.

2. All these drugs have produced dangerous, often fatal, blood dyscrasias, the lowest incidence having occurred with Dilantin.

3. Evidence is presented to indicate that periodic blood counts are of little aid in reducing the morbidity or mortality of blood dyscrasias due to drugs.

4. It is considered that the therapy of first choice is Dilantin, alone or with phenobarbital. The other drugs should be used only after careful consideration, with the knowledge that occasional fatalities may be anticipated.

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• As regards other remedies for epilepsy, I have but little to say. Belladonna has never in my hands produced the least effect, neither has digitalis, nor indigo, nor cotyledon umbilicus, nor any of the salts of copper. I might say the same thing of the other so-called remedies. Hydrate of chloral in three cases mitigated the frequency of the paroxysms, but only for a short time. In several other cases it was without effect; Calabar bean was slightly beneficial in one case.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

# Neurology

## Clinical Pathologic Conference

From the Division of Neurology, Minneapolis Veterans Hospital, and the University of Minnesota

*Presented by Maynard M. Cohen, M.D. and A. B. Baker, M.D.*

PRESENTATION OF CASE

DR. COHEN: A 54 year old male, a motor launch operator, was perfectly well until onset of his present illness which occurred on June 1, 1950. At that time he first experienced some dizziness and a sharp, knife-like pain on the right side of his head and forehead while he was bending over cleaning paint brushes. This pain persisted for a half hour, at which time he was given an analgesic by his local physician. The patient was then symptom free for two months. On July 30 the pain recurred and radiated across the right eye to the middle of the face, lasting six hours. He again received an analgesic with some relief. The following morning the patient first noted numbness on the right side of the face. Neurologic examination revealed a diminished corneal reflex on the right, a hypalgesia and hypesthesia of the right side of the face and forehead, and positive Babinski, Oppenheim and Gordon signs on the left. The remainder of the neurologic examination was normal. At this time the patient was admitted to the hospital.

DISCUSSION

DR. BAKER: Even at its onset, this case presents a number of interesting features of diagnosis and localization. From the standpoint of localization, this case is relatively clearcut. The specific involvement of the fifth cranial nerve on the right points definitely to a pontine lesion. However, the fifth nerve could be involved either within the pons or more peripherally after it leaves the brain stem. A number of diagnostic possibilities must be considered in view of the early and apparently isolated unilateral involvement of the fifth cranial nerve. Among the various conditions which merit consideration are: 1) an early tic douloureux or trifacial neuralgia; 2) a herpes zoster; 3) a neoplasm of the

Reviewed in the Veterans Administration and published with the approval of the chief medical director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

fifth nerve such as a neuroma; 4) an aneurysm of some of the vascular structures along the base of the brain; and 5) tumors or infections in or about the petrous portion of the temporal bone or the middle cranial fossa. In attempting to limit the diagnosis more carefully, the only lead one has is the associated involvement of the pyramidal system. This would indicate that the lesion, even at this time, is closely adjacent to the pons and is probably not situated more peripherally. This involvement of the contralateral pyramidal tract along with the ipsolateral fifth cranial nerve produces a typical crossed hemiplegia syndrome. This type of syndrome eliminates a diagnosis of tic douloureux and probably also of herpes zoster. The fluctuating nature of the symptoms would make one hesitate in the diagnosis of a neoplasm. In view of the crossed hemiplegia, the acute onset and the fluctuating nature of the findings, one would feel more inclined at this point to consider some kind of a vascular lesion involving the right side of the brain stem.

CASE HISTORY *continued*

DR. COHEN: The day following admission to the hospital, the patient began to complain of a severe headache in the back of the neck radiating to the vertex. This was accompanied by vomiting. The neurologic examination revealed early choked disks bilaterally. The right corneal reflex was diminished, but sensation over the face appeared to be normal. The patient had a slight stiff neck. The left triceps reflex seemed slightly greater than the right. The left abdominal reflexes were absent, and there was a suggestive positive Babinski sign on the left. Speech was slurred and incoherent. The patient's blood pressure was 158/88. The remainder of the examination was difficult to accomplish because of the patient's inability to cooperate. However, no apparent abnormalities were found in the general examination of the head, neck, thorax and abdomen. At 3:30 p.m. that afternoon, the patient became deeply comatose and the papilledema became more noticeable bilaterally. He had a marked nuchal rigidity and Cheyne-Stokes respiration. The systolic blood pressure at this time rose to over 200 mm. The pulse rate was 40.

DISCUSSION *continued*

DR. BAKER: It is apparent from the course of this patient's illness that marked changes had suddenly occurred within the lesion. The focal findings actually had not changed, but the general symptomatology was altered dramatically. A number of explanations can be offered for this rapid downhill course depending upon the possible nature of the patient's lesion. If this patient has a vascular lesion in the form of an aneurysm of one of the basilar vessels, then a rupture with bleeding could account for the nuchal rigidity and the radiating pain down the back of the neck. Blood in this region could obstruct the basilar cisterns and interfere with proper cerebral spinal fluid flow resulting in a rapid increase in intracranial pressure. On the other hand, if this patient has a neoplasm in this region, it is possible that a sudden herniation into the foramen magnum could likewise produce the nuchal rigidity, interfere with the proper cerebral spinal fluid drainage producing a rapid increase of intracranial pressure, and result in the many medullary symptoms that this patient presents. Regardless of the exact nature of the complication, it is apparent at this time that this patient has now become an acute medical emergency, and that some attempt must be made to relieve the increased intracranial pressure in order to alleviate the patient's symptoms.

CASE HISTORY *continued*

DR. COHEN: Because of the patient's critical condition, a ventriculostomy was performed at 5:00 p.m. on August 1. A tube was inserted into the right lateral ventricle. The cerebral spinal fluid obtained through the ventriculostomy was tinged with blood. Following this procedure the patient became less restless, but his blood pressure remained elevated. The patient improved slightly during the next two days; on August 3 an angiogram was attempted on the right side. Only the vessels of the anterior portion of the circle of Willis and its branches were filled and no abnormality was demonstrated, however. On August 5 the ventriculostomy tube was removed, and the patient tolerated this procedure fairly well. However, on August 16 he became more lethargic and uncooperative. The right trephine area was again aspirated and 60 to 70 ml. of xanthochromic fluid were removed. On August 18 a little air was injected into the ventricles. At this time the ventricular fluid was clear but under increased pressure, and the ventriculogram revealed bilateral diffuse hydrocephalus. The patient remained lethargic. His course continued progressively downhill.

DISCUSSION *continued*

DR. BAKER: The presence of blood tinged fluid at the ventriculostomy would indicate that a vascular lesion was the most probable of our original diagnostic considerations. The exact nature of such a vascular lesion can now be considered. The earliest symptoms of a crossed hemiplegia are focal in nature and suggest some form of a tumor mass such as an aneurysmal dilatation. The subsequent course with pain in the back of the neck, stiff neck, and medullary compression indicate bleeding from such an aneurysm into the region of the brain stem. It is a little difficult to explain exactly how this blood reached the lateral ventricles. It is possible that there was some retrograde contamination of the ventricular fluid from the basilar bleeding. It is also possible, however, that the blood tinged fluid obtained on ventriculostomy was unrelated to the pathologic process and was incidental to the surgical procedure. The results of angiography are not surprising. It is apparent that this patient's lesion is in the posterior fossa, and to demonstrate such a vascular lesion angiography would have to be done through the vertebral artery rather than through the internal carotid. The presence of a hydrocephalus on ventriculogram is merely corroborative evidence of an obstruction produced by the vascular hemorrhage.

CASE HISTORY *continued*

DR. COHEN: On August 22 a suboccipital craniotomy was done. Dye was then injected into the lateral ventricles and it appeared quickly in the cisterns. Since no obstruction was apparent, the operative wound was closed and a Penrose drain and ventriculostomy tube were left in place. The drain was removed on the first postoperative day, and the ventriculostomy tube was removed on the second postoperative day. On August 24, two days later, the patient developed a pneumonitis which responded to chemotherapy. By September 5 the patient's condition was worse and he was having severe respiratory difficulty. He was maintained on symptomatic treatment for approximately a month until October 2, when he developed a generalized seizure. His respirations became more irregular. By December 28, he had developed severe hiccuping, his pulse was rapid and irregular and respirations were labored and shallow. The patient expired on January 11, 1951, having been completely unconscious and unresponsive during the last three months of his life. Throughout this period, he showed constant evidence of marked increased intracranial pressure which could only be relieved temporarily by drainage and subtemporal decompression. Through-

out his stay in the hospital, a large number of laboratory tests were taken all of which proved to be within normal limits.

SUMMARY

DR. BAKER: In reviewing the clinical aspects of this case, one feels fairly comfortable about the pathogenesis of the disease process. At the onset it was apparent that this patient had a small lesion in the right pontine region involving the fifth cranial nerve and compressing the pontine structures to produce a crossed pyramidal tract involvement. The acute onset and periodic nature of the complaints, as well as the proximity of the lesion to the brain stem, suggested a vascular lesion as one of the primary considerations. A vascular lesion which could produce such pressure symptoms immediately suggested an aneurysmal process involving some branch of the basilar system. The course of illness following the initial onset contributed additional evidence to this original consideration. The sudden appearance of headache, stiff neck and increased pressure is almost diagnostic of a subarachnoid bleeding, and pointed strongly to a rupture of the aneurysm into the basilar region. This concept was strengthened by the appearance of blood tinged fluid on ventriculostomy and by the gradual appearance of a diffuse hydrocephalus on ventriculogram. The subsequent course appeared to be due to an obstruction in the cerebrospinal fluid drainage, no doubt the result of the location of the lesion rather than its severity. One might speculate that the vascular lesion had somehow blocked the basilar cisterns and thus prevented proper drainage of spinal fluid. We were unable to combat this complication in spite of the various procedures instituted. It is unfortunate in this case that a vertebral angiogram was not accomplished since such a procedure had the greatest likelihood of demonstrating the lesion.

AUTOPSY AND PATHOLOGIC FINDINGS

DR. COHEN: The principal lesion observed at postmortem examination was an aneurysm of the right superior cerebellar artery (figure 1). This aneurysm was directly adjacent to the right fifth nerve as it emerges from the pons. The aneurysm measured 1.5 cm. by 1.5 cm. by 1 cm. It was attached to the right superior cerebellar artery by a narrow stalk and the continuity of the superior cerebellar artery was not interrupted by the aneurysm. The original area of rupture was not visualized. On sectioning the vessel, the lumen was filled with a firm, deep red, adherent thrombus through which ran a small lumen measuring up to 0.2 cm. in maximal diameter. Over the base of the brain, there was a yellowish brown discoloration which was most prominent in the immediate vicinity of the aneurysm. There was a compression of the underlying pons by the aneurysm. Coronal sections of the cerebral hemispheres revealed a marked dilatation of the ventricles.

Microscopic examination of the aneurysm revealed the lumen to be small and surrounded by strands of loose fibrin, containing enmeshed red blood cells, white blood cells and occasional macrophages filled with light brown pigment. The media of the aneurysm consisted of fibrous connective tissue, and at one margin there was a thinning of the media with fragmentation of the connective tissue fibers. Within the adventitia, there were lymphocytes, plasma cells and aggregates of macrophages containing light brown pigment.

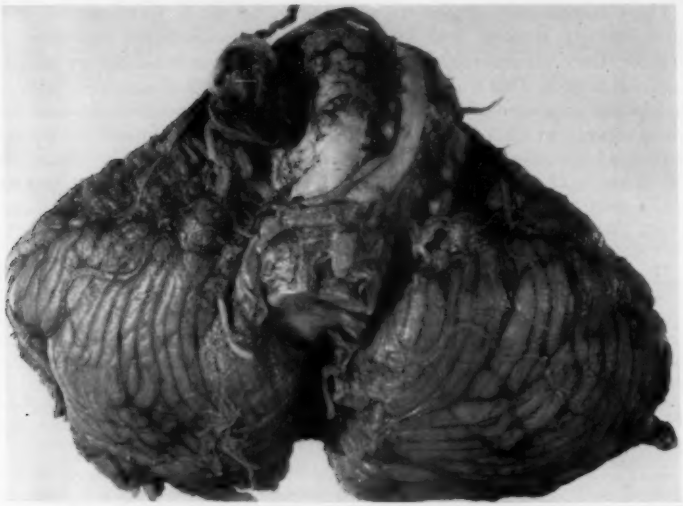

FIG. 1. Specimen of cerebellum and brain stem exhibiting aneurysm of the right superior cerebellar artery which has been opened to demonstrate a thrombus within the lumen. Note the indentation of the underlying pons.

GENERAL DISCUSSION

DR. COHEN: Aneurysms of the brain are chiefly extracerebral and generally occur on the main trunks of the circle of Willis. These aneurysms occur at all ages, the majority occurring in individuals between the ages of 20 and 50 years. Their frequent presence at the angle of bifurcation of the vessels has led to the belief that they are generally due to some congenital defect and in a large number of these cases the media has been completely absent in these areas (Forbus[1]). Dandy[2] and Bassett[3] felt that these aneurysms arise in areas representing remnants of embryonic vessels which normally completely disappear and that these remnants remain to form the body of the aneurysm. Aneurysms are found with the greatest frequency in the anterior portion of the circle of Willis but all parts of the vascular tree may be involved. About half of all aneurysms are located on the internal carotid or middle cerebral artery, about 15 per cent on the anterior communicating artery and about 10 per cent on the anterior cerebral artery. Only about 25 per cent are found posterior to the internal carotid artery, and most of these arise at the junction of the basilar with the posterior cerebral or the posterior communicating arteries. Aneurysms generally are not found on vessels arising within the substance of the brain. Aneurysms of the superior cerebellar artery, as reported in this case, are of extremely unusual occurrence, only three having been reported in the literature (MacDonald and Korb[4]) (French and Blake[5]).

Aneurysms usually produce their symptoms either by compression or by rupture. The compressive symptoms result from pressure on the cranial nerves and/or the adjacent parenchy-

ma. These compressive symptoms are frequently very striking and focalizing, since they commonly implicate the cranial nerves. This was well illustrated in the present case with a very select involvement of the fifth cranial nerve, which specifically localized this lesion to the mid portion of the pons. The symptoms of rupture are classical and generally consist of severe headache, occipital pain, nuchal rigidity, loss of consciousness and occasionally evidence of increased intracranial pressure. These symptoms were very dramatically evident in the present case. When the clinical symptoms and signs usually occurring with cerebral aneurysms are considered, it becomes apparent that the present case was fairly typical.

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• On looking at the base of the brain we notice many white cords or threads, apparently coming from the brain, and in pairs, or one from each hemisphere. These are called the cerebral nerves, and are numbered First, Second, Third pairs, reckoning from the anterior to the posterior part of the brain. Some anatomists enumerate but nine pair of cerebral nerves, others eleven and twelve. This difference among authors respecting the number of cerebral nerves, arises from some considering the seventh pair, consisting of the facial and auditory, as two pairs instead of one; and the glosso-pharyngeal and pneumo-gastric, which by some are called one pair, are by others divided into two. Some consider the spinal accessory as an associate of the pneumo-gastric and glosso-pharyngeal. I shall treat of twelve distinct pair of cerebral nerves. Viz.: 1. Olfactory. 2. Optic. 3. Oculo-muscular. 4. Inner-oculo-muscular, or pathetic. 5. Trigeminal. 6. Abducentes. 7. Facial, or portio-dura. 8. Auditory, or portio-mollis. 9. Glosso-pharyngeal. 10. Pneumo-gastric, or par-vagum. 11. Lingual, or hyo-glossal. 12. Spinal-accessory.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

# NEWSLETTER

MAY, 1951

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Howard D. Fabing, President-Elect
Walter O. Klingman, Vice-President
Francis M. Forster, Secretary
Joe R. Brown, Treasurer

AMERICAN ACADEMY OF NEUROLOGY

**Virginia Beach Compendium** In the gay, easy setting of the Cavalier Hotel, Virginia Beach, Academy members and their friends gathered April 11-13 to make the second biennial meeting of the AAN a milestone in the history of American neurology. Boasting an attendance of 405, it was the largest meeting to date since the organization of the Academy in 1948. The meetings were preceded by a review course in neuropathology and ended in a joint session with the American chapter of the International League Against Epilepsy. Scientific and executive sessions, complemented by lively social activities, re-emphasized the central theme of the Academy: to broaden the scope and influence of neurology and to unite neurologists in friendly entente.

**Pres. Baker Looks at the Past and Future** In a bold and forthright presidential address before AAN members and the Women's Auxiliary, A. B. Baker reviewed past accomplishments and future potentials. Extolling the achievements of his various committees and pointing to the phenomenal growth of the Academy within three years, he stated, "This society already has taken its place as a vital and dynamic force in American medicine and in world neurology." But, according to Dr. Baker, the work has only begun. A still greater and more cooperative effort is needed from AAN members and the auxiliary to place neurology in its proper position in universities, government agencies and in the practice of medicine.

**1952 Meeting to be Held at Louisville** The next meeting of the Academy will be held at Louisville, Kentucky, in the Brown Hotel April 24 and 25, 1952....Deadline for titles and abstracts of papers to be presented at the meeting is November 1st, 1951. Titles should be submitted to Dr. A. T. Ross, chairman of the subcommittee on scientific meetings. His address is Indiana University School of Medicine, Indianapolis, Indiana.

**Sebrell Address on NINDB** William H. Sebrell, Jr., medical director of the National Institute of Health, U. S. Public Health Service, gave a special address before the AAN meeting, describing the organization and history of the National Institute of Health with particular reference to the new National Institute of Neurological Diseases and Blindness. Though originally envisioned by Harvey Cushing shortly after World War I, the institute did not come into being until 1950....Stressing the importance of the Academy in the formation of this institute, Dr. Sebrell said he was proud of the Academy's close association with it. Establishment of this institute indicates the increasing awareness on the part of the Public Health Service of the importance of neurological diseases in the nation's

health. This institute, though working closely with psychiatry, is independent of it as far as its approach is concerned....Dr. Sebrell emphasized the importance of neurologic research as well as training, and predicted a bright future for the institute although quick results cannot be expected at this time owing to the defense obligations before Congress.

**Neuropathology Course Starts a Trend** The two day review course in neuropathology preceding the meeting proved a signal success. More than that, it set in motion a trend to develop teaching collections and organize special courses within the framework of the Academy for the benefit of its members. AAN members of the faculty in neuropathology at Virginia Beach included A. B. Baker, F. M. Forster, Webb Haymaker, A. L. Sahs, A. T. Steegman and Fae Y. Tichy.

**Scientific Sessions Broad in Scope** The scientific program presented a carefully selected collection of papers dealing with neurology in its structural, dynamic and therapeutic aspects, many of which will appear in forthcoming issues of NEUROLOGY. The sessions were under the direction of such skillful moderators as Wartenberg, Simon, Mackay and Hoefer. Contributors of papers to the scientific sessions hailed from 17 different states distributed as follows: Ohio (5), New York (5), California (4), Minnesota (3), New Jersey (2), Connecticut (1), Florida (1), Illinois (1), Iowa (1), Kentucky (1), Maryland (1), Massachusetts (1), Michigan (1), Oklahoma (1), Pennsylvania (1), Washington (1), Wisconsin (1)....Intervals between sessions allowed for the demonstration of scientific exhibits and two Veterans Administration motion picture films—one on epilepsy, the other on aphasia. Of particular interest was an exhibit by R. Wartenberg displaying a complete collection of 76 current journals from all over the world devoted wholly or in part to neurology....

**Executive Sessions Shape Policies** Academy committees had breakfast conferences throughout the sessions. The recommendations of these committees were presented to the membership during two executive sessions, Pres. A. B. Baker presiding. Significant recommendations will be reported in the next issue of the Newsletter.

**New Officers Elected** The following new Academy officers were elected for 1951-1953: Pearce Bailey, president; Howard D. Fabing, president-elect; Walter O. Klingman, vice-president; Francis M. Forster, secretary; Joe R. Brown, treasurer. Titus H. Harris and T. J. C. von Storch were elected members of the board of trustees....The Women's Auxiliary elected Mrs. Frederick P. Moersch, president; Mrs. A. B. Baker, president-elect; Mrs. Franklin O. Meister, vice-president; Mrs. D. B. Ruskin, treasurer.

**Social Sidelights** The warm friendliness of the social activities of the meetings will long be remembered by those who were at Virginia Beach. The gala occasions were the Academy cocktail party and banquet followed by dancing. In addition to these official functions there were several informal parties

among smaller groups. The tempo and congeniality of the social affairs was stepped up by the special committee of hosts and hostesses whose business it was to encourage introductions and pave the way for lasting friendships....The sports tournaments brought forth an array of talent, and prizes were awarded to winners.

**AAN Diplomas Now Available** Members desiring certificates of membership should forward a written request to the American Academy of Neurology, 19 Millard Hall, University of Minnesota, Minneapolis 14, Minn. Included in the request should be the member's name as he wishes it to appear on the certificate and a check for $2.00 to cover costs.

* * * * * *

**Ulster Irish Society Honors Foster Kennedy** In New York's Waldorf-Astoria on March 9, the Ulster Irish Society awarded to Foster Kennedy their annual Medal for Notable Service to the Nation. Prior to the presentation of the award a pithy account of the life and work of Dr. Kennedy was given by Lewis Stevenson, his first resident on the Bellevue Neurologic Service.

**M. S. Society Holds Annual Meeting** The fourth annual meeting of the National Multiple Sclerosis Society was held in New York on March 13. This society now represents over 16,000 members in the United States and in every foreign country. Of the nine leading voluntary health agencies it ranked first in the percentage of funds raised and applied directly to research in 1948 and 1949. Cornelius H. Traeger, medical director of the society, is also a member of the National Institute of Neurological Diseases and Blindness Council.

**Personal Course in Cerebral Palsy** The Cook County Graduate School of Medicine announces that the two-week personal course in cerebral palsy, given by Dr. M. A. Perstein and associates, will be held this year, July 9-21. This intensive didactic clinical course in cerebral palsy is intended primarily for neurologists, pediatricians, orthopedists, physiatrists and psychiatrists. All communications concerning the course should be directed to the Cook County Graduate School of Medicine, 427 South Honore Street, Chicago 12, Illinois.

**Neurology in Texas** The Lone Star State, flush with money for things medical and useful, is developing gradually an expansive neurologic program. Thomas Farmer is organizing a service at Southwestern Medical School in Dallas. William F. Fields, professor of neurology at Baylor University in Houston, has a growing department affiliated with the Veterans Houston Hospital. There is a vacancy for an additional resident in this program. Dr. Fields also visits at the Bluebird Epilepsy Clinic. W. G. Lennox, who recently held several conference clinics in this area, comments most favorably on their epilepsy program.

**Haymaker Surveys German Collections** Webb Haymaker has returned from a two months' survey of the status of German collections in neuroanatomy and neuropathology. A good part of the survey was devoted to the collections of Oskar and Cecile Vogt, but he also visited the laboratories of Spatz and Hallervorden in Giessen, Scholz in Munich, Hans Hoff and others in Vienna.

* * * * * *

**New Epilepsy Clinic Opens at Georgetown** The newly established department of neurology at Georgetown University has opened (Jan. 6, 1951) an epilepsy clinic as an important unit in the out-patient department of Georgetown University Hospital. The Georgetown epilepsy program also includes a research project on temporal lobe epilepsy, sponsored by the U. S. Public Health Service.

**Briefs** The annual Institute on Neurology and Psychiatry of the Medical College of the State of South Carolina was held in Charleston (March 19-21) with Prof. Olin B. Chamberlain presiding. Among the lecturers were F. H. Allen, Pearce Bailey, Francis C. Grant and L. B. Kalinowsky....A. B. Baker and W. O. Klingman conducted discussions on neurologic topics in a seminar for hospital psychiatrists at the VA Hospital, Topeka, Kansas (April 3)....The University of Michigan is giving a postgraduate course in clinical neurology at Ann Arbor (May 14-17) ....The Beth Israel Hospital in New York is opening a new neurologic service (July 1, 1951) under the direction of Samuel Brock....The VA Hospital at Lyons, N. J., held its first annual institute in psychiatry and neurology (April 18) under the aegis of its Manager, Crawford N. Baganz, and the New Jersey Neuropsychiatric Association. Among the speakers were H. Houston Merritt, H. C. Solomon and S. B. Wortis....

Pearce Bailey

# Neurology

## BOOK REVIEWS

### The Cerebral Circulation in Health and Disease

*Carl F. Schmidt, M.D. 1950. Springfield, Illinois: Charles C. Thomas, 78 pages, $2.00.*

Popularization of the more recent therapeutic approaches to the problem of cerebral vascular disease has made it necessary for the neurologist, neurosurgeon and medical practitioner to review available information on the physiology of the cerebral circulation. Dr. Schmidt has fulfilled this need admirably in the present monograph.

Following a brief review of the anatomical problems involved in cerebral circulation, the author discusses in some detail the influence of vasoconstrictor and vasodilating nerves on cerebral circulation. The effects of drugs, hormones and metabolic products are next considered. Much of the material in these sections has heretofore been of theoretical interest, primarily, but with the more recent use of vasodilating drugs in the treatment of cerebral vascular disease, the material in these sections is of fundamental practical value.

The final section is concerned with the application of physiological methods to the study of cerebral circulation. Dr. Schmidt writes critically concerning many of these methods and creates the impression that the method developed by Kety has made possible "the quantitative measurement of cerebral blood flow and cerebral metabolism in intact man." He then goes on to cite some of the clinical situations in which this technique has been applied. These include studies of schizophrenics, epileptics, brain tumor patients, hypertensive patients and a small group of postfrontal lobotomy cases.

This short but well organized and informative monograph can be recommended to all who are concerned with either the clinical or laboratory problems of cerebral circulation.

A. L. D., JR.

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### Recovery from Aphasia

*Joseph M. Wepman, Ph.D. 1951. New York: The Ronald Press Company, 276 pages, $4.50.*

Dr. Wepman, a speech pathologist, has written a comprehensive approach to the problem of aphasic retraining. According to the author, "language should be considered as the means of interpersonal relations, not the end result of recovery." Inasmuch as the present book is written pri-

marily for speech therapists, this emphasis upon the need for total personality adjustment is an excellent one.

The early chapters of the book are concerned with a brief but comprehensive review of the history of the theoretical aspects of aphasia. Most of the major contributions to the field from Broca through Goldstein and Neilsen are briefly noted. Dr. Wepman, expressing his own viewpoint, states that "aphasic language disorders are considered as affecting all the language modalities and cannot be limited to specific language skills. The recovery process must include a program leading to reintegration of the activity of the cortex and not to specific skills."

The author points out the consistent, but rather low positive correlation between the aphasic patient's pre-morbid educational level and his relative rank order in terms of language ability following the onset of aphasia. He suggests that it might be possible to predict the amount of loss and gain an individual would have were he to suffer a brain injury. The results achieved with aphasic adults in this re-education program indicate, according to the author, that the language problem can be materially reduced.

Dr. Wepman stresses the need of a total program to include psychotherapy as well as recreational, social and occupational programs. He calls much needed attention to the "non-language characteristics of aphasics" as seen in behavioral manifestations other than those primarily attributable to the brain damage. A review of this portion of the book has potential value to all who deal with aphasics and brain injuries of any type.

A review of the literature concerning aphasia following right brain damage in the lefthanded is most interesting. The author himself states that of 696 brain damage patients seen by himself, some 47 had a left hemiplegia, but none had any residual aphasia. He goes on further to state that review of data from his files shows that not a single case of aphasia had been seen following right brain damage regardless of handedness. He then reviews the literature concerning this subject and states that "the conclusions to be drawn from this observed material, which seem to deny an old and strongly held postulate concerning cortical function, are twofold: first that language deficits following damage to the right hemisphere either are of the nature of dysarthrias or, if aphasia-like, last only a short time and are overcome spontaneously; second that permanent aphasia, the propositionalizing disorder of symbolization in language, occurs only after injuries to the left cerebral hemisphere, regardless of cortical dominance." If these observations prove to be correct, reconsideration of the problem of cerebral dominance and its assured relation to aphasia will be necessary.

The third and final section of the book is concerned with a program for training of aphasia therapists and associated non-language therapists needed in the treatment of aphasic patients.

Although written largely from a nonmedical point of view, there is much material in this book of interest to the professional neurologist, neurosurgeon and psychiatrist. The early section of the book may prove repetitious to the professional neurologist, but the latter part with its suggestions for practical management cannot fail to be helpful.

A. L. D., JR.

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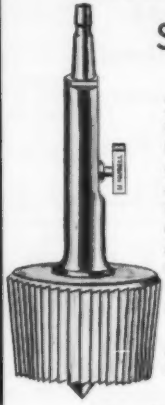

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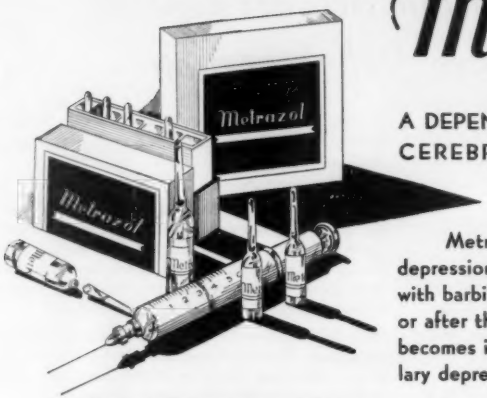


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# *Complete Epileptic Seizure-control; First Step in Rehabilitation*

In the drug therapy of the epileptic, nothing short of *complete* suppression of seizures can rightly be called full success. Complete seizure-control is a prerequisite to the patient's return to a normally active life. Carter[1] states: "Basically all efforts should be directed toward preventing seizures and the tendency to chronic invalidism."

The management regimen should include:[2]

I. Good physical and mental hygiene.
   a) Wholesome diet; Regular bowel habits; Avoid noxious materials, e.g. alcoholics; Moderate physical activity.
   b) Help overcome feeling that epilepsy is shameful; Encourage normal work and recreation; Regular sleep without overprotection.

II. Anticonvulsant medication selected on the basis of Exact Diagnosis:
   "Certain drugs are more effective in one type of seizure than they are in another, and it is necessary to use proper drugs. The dosage must be individualized for each case."[3]

Thus, the best guide in selecting medication for a patient is the type of seizures present. (Frequently several drugs in combination is most effective.)

The table shows which drugs are indicated for each type of seizure. It will be noted that the newer hydantoin, Mesantoin, is effective for *grand mal*, Jacksonian and focal seizures.

MESANTOIN DOSAGE is adjusted to the lowest level adequate to attain freedom from seizures. Start with ½ or 1 tablet daily during the first week; increase the daily intake by ½ or 1 tablet during the next week. Continue this up to optimal dosage. When another drug has not given good results, Mesantoin is added by the same procedure; then the old drug is gradually reduced.

SIDE EFFECTS — Mesantoin produces side effects in some cases: Skin and blood changes are signs of sensitivity — the drug should be discontinued. Drowsiness develops upon reaching maximum dosage.

PRECAUTIONS — Certain precautions are necessary to minimize untoward effects.

a. close check on patient — repeated visits and blood counts.
b. No Mesantoin, if white cell count below 4000.
c. caution if (1) rash or blood changes.
   (2) History of drug sensitivity.
d. discontinue drug if (1) bleeding of gums or vagina.
   (2) Sore throat

| TYPE OF EPILEPSY | PRIMARY CLINICAL MANIFESTATIONS | MEDICATION | AVERAGE ADULT DAILY DOSE★ | LIMITING SIDE EFFECTS | SIGNS OF SENSITIVITY |
|---|---|---|---|---|---|
| GRAND MAL | Aura followed by loss of consciousness; tonic-clonic convulsions and autonomic disturbance, e.g., in bladder function. | Phenobarbital | 1½ grs. h.s. Usual max.: 3 grs. per day | Sleepiness | |
| | | 5,5 diphenyl hydantoin | 1½ grs. t.i.d., p.c. Usual max. 6 grs. per day | Diplopia, staggering (may increase petit mal) | Overgrowth of gums, body hairs; itching rash on extremities, gastric irritation |
| JACKSONIAN | Convulsions begin in one area and spread outwards (Jacksonian march.). No loss of consciousness.[3] | 3 methyl 5,5 phenylethyl hydantoin (mesantoin) | Adults: 2 to 6 tabs. Children: 1 to 4 tabs. | Sleepiness | Full details given; see Psychomotor cross-column below |
| | | phenylacetylures[5] | 2 Gms. per day. Max. dose 6 Gms. per day[4] | Drowsiness[5] | Central nervous system affected, nausea, vomiting and abdominal pain[5] |
| PSYCHO MOTOR | Period of amnesia; actions apparently purposeful but mechanical; incoordination. Mild tonic spasms. In children: "behavior problems".[3] | 3 methyl 5,5 phenylethyl hydantoin[4] | Adults: 2-6 tabs. Children: 1-4 tabs. | Pharyngitis, mucous membrane bleeding, lymphadenopathy, measles-like rash with itching and fever; in severe reaction: blood dyscrasia. | |
| | | phenylacetylurea[5] | See phenylacetylures—above | | |
| PETIT MAL TRIAD | Attacks: in series (rapid succession), abrupt onset, few sec. duration; no aura nor impairment of consciousness. Rhythmic twitching (e.g. eyelids). | 3,5,5 trimethyl oxazolidine 2,4 dione | 0.9 to 1.2 Gms. | Inability to see in a bright light. Drowsiness | Hiccough, acneform rash, leukopenia |
| | | N methyl derivative of phenobarbital | 6 grs. | Sleepiness | |

★Although an average daily dose can be stated for each of these drugs, to obtain best results it is necessary that the physician determine the dose required by each individual patient for maximum control of his seizures.

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# "Good to excellent results with PROTAMIDE"

## . . . In 28 Cases of HERPES ZOSTER at Bethesda Naval Hospital*

William C. Marsh, Commander (MC) U.S.N., in a currently published paper[1], "Treatment of Herpes Zoster with Protamide," now available to physicians as a reprint, presents these findings:

"Thirty-one cases of herpes zoster were treated with Protamide. Good to excellent results were obtained in twenty-eight. In those failing to respond other factors besides age of patient may have been involved.

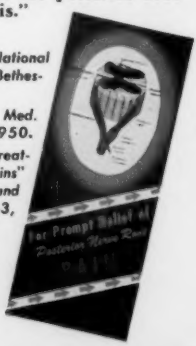
"No controls were in our study as thousands of intramuscular injections of other drugs given to patients with herpes zoster in the past, with no appreciable benefit, would adequately serve as a control.

"Pain, not merely the discomfort or itching, was the indication for treatment. Protamide (1.3 cc, the contents of one ampul) was given daily intramuscularly. No other local or systemic medications were given.

"The relief of pain was superior to that obtained when using either pituitrin, thiamine chloride, autohemotherapy, sodium iodide, or high voltage Roentgen therapy.

"The advantages of Protamide are the simplicity and absence of pain in administration, lack of reactions, and apparent safety.

"Costello[2] found that Protamide was effective in the relief of the posterior root pain of tabes dorsalis."




* *U. S. Naval Hospital, National Naval Medical Center, Bethesda, Maryland.*

*1. U.S. Armed Forces Med. Journal, September, 1950.*

*2. Costello, R. T. New treatment for "lightning pains" of tabes dorsalis, Urol. and Cutan. Rev. 51: 260-263, May, 1947.*

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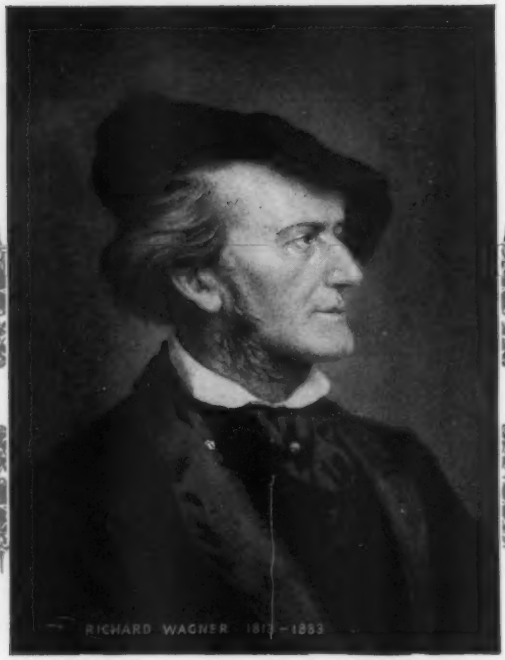


# *Psychoneurotics of Genius*

**Psychoneurotic traits — unbalanced emotional reactions, moods, ill temper and irresponsibility — are not uncommon among men of genius. Richard Wagner, great dramatic composer, had the emotional stability of a six-year-old throughout his adult life.**

**In many instances mild sedation has to be provided before a person of psychoneurotic make-up can achieve emotional stability. Mebaral combines a high degree of sedative effectiveness with a relative freedom from side effects such as languor and drowsiness. Patients usually become calmer, more cheerful and better adjusted to their surroundings without clouding of mental faculties. Average sedative dose: Adults, 32 mg. to 0.1 Gm. (½ to 1½ grains) three or four times daily. Children, 16 to 32 mg. (¼ to ½ grain) three or four times daily. Tablets ½, 1½ and 3 grains.**

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